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ON SPONTANEOUS PNEUMOTHORAX¹

By KENNETH M. A. PERRY

(From the London Hospital)

With Plates 1 and 2

BETWEEN the years 1924 and 1937 there have been 114 cases of spontaneous pneumothorax diagnosed clinically in the London Hospital. Thirteen were symptomatic of some gross lesion, i.e. seven following trauma, three complicating lung abscess, and one each empyema, carcinoma of oesophagus, and malignant neoplasm of heart. Sixteen cases arose complicating chronic pulmonary tuberculosis, and of these nine died within one month, a mortality rate of 56 per cent. The remaining 85 cases arose spontaneously in apparently healthy persons. This latter type might be named Benign Spontaneous Pneumothorax.

Aetiology of Benign Spontaneous Pneumothorax

Several explanations of the occurrence of this condition have been put forward by many writers. The following are the most important:

1. Ulceration of the visceral pleura by a subpleural tubercle.
2. Rupture of an air vesicle on the surface of the lung. This may have been produced in any of the following ways:—
 - (a) Generalized emphysema.
 - (b) Localized emphysema, scar-tissue vesicle formation in the lung, or subpleural bleb.
 - (c) Congenital cyst.
3. Rupture of a pleural adhesion tearing the visceral pleura.
4. Rupture of the visceral pleura as a result of sudden effort or awkward posture.

1. *Ulceration of the visceral pleura by a subpleural tubercle.* Fishberg (1932) states that 'The origin of this form of pneumothorax has been discussed by many writers. The consensus of opinion is that the vast majority are caused by a tuberculous lesion in the lung or pleura; it is maintained that at least 90 per cent. originate thus. The rent in the pleura may be due to softening and consequent perforation of a subpleural tubercle. Further experience with this sort of pneumothorax has shown that a large proportion is due to distinctly non-tuberculous causes. In the writer's opinion probably 20 per cent. of cases of really spontaneous pneumothorax are not due to tuberculosis.'

¹ Received August 6, 1938.

It has been generally accepted that tuberculosis is the commonest cause of spontaneous pneumothorax. Even the extensive American work edited by Tice (1932) states that 90 per cent. of cases of spontaneous pneumothorax are due to this cause. Satisfying though this theory may appear at first sight, there do not appear to be any facts to substantiate it. Nearly all cases of spontaneous pneumothorax show a complete absence of all the usual symptoms and signs of tuberculosis. As Olbrechts (1930), and Kjaergaard (1932, 1935), and others have stressed, these cases distinguish themselves by the absence of fever, and after the initial shock, by their normal pulse-rate. This is important evidence against a tuberculous origin, and contrasts very strongly with that other pleural lesion, an acute effusion, which nearly always shows these points and is frequently tuberculous in origin, and with the cases occurring in known tuberculous subjects which always run a febrile course. Patients with benign pneumothorax rarely have a cough, and still more rarely any sputum. In no case in the present series have tubercle bacilli been found in the sputum, even after guinea-pig inoculation, a finding in agreement with other writers on this subject.

Investigations into the skin tuberculin reactions by Zinn and Siebert (1929), Koelenschmidt (1926), Friesdorff (1927), and Olbrechts (1930) have revealed them negative in many cases. The present series includes a child aged 4 years who developed a pneumothorax during an attack of whooping cough, and was found to have a negative Mantoux reaction. Olbrechts states that the blood sedimentation-rate was not altered during the disease in four of his cases in which the test was performed; and this was also the case in three of the present series. Other cases with a normal sedimentation-rate have been recorded by Oeschli and Miles (1934), Rossel (1935), and Willis (1937). The rupture of a caseous focus into the pleural cavity invariably infects it, causing either a hydro- or pyo-pneumothorax with fever; this is also the case when a spontaneous pneumothorax is superadded to an artificial one. The benign pneumothorax is distinguished by the fact that it is always dry, or at the most contains only a few drachms of fluid. There is no case reported in which, at autopsy, one of these minimal subpleural tubercles has been found giving rise to a pneumothorax. Evidence in favour of the tuberculous aetiology of this condition may be sought in the later course of such patients. Pleural effusions are believed to be tuberculous very largely on the evidence of their subsequent history; and if tuberculosis were the usual cause of spontaneous pneumothorax, a considerable proportion would show evidence of that disease subsequently. In the present paper an attempt has been made to follow up the 85 cases of this disease which have been in the London Hospital in the years 1924 to 1937, and to discover how many of them had had subsequent pulmonary tuberculosis. Fifty-five cases have returned to hospital and been examined clinically and radiologically. They have not shown any evidence of subsequent pulmonary tuberculosis, and a further 12 have been traced and found to be alive and well at the present time.

The results of this investigation are set out in the following table:

| Year. | No. of patients. | Traced and X-rayed. | Traced. Alive and well. | Traced over a period. | Traced. Dead. | Died in hospital. | Un-traced. |
|--------|------------------|---------------------|-------------------------|-----------------------|------------------|-------------------|------------|
| 1924 | 2 | 1 | — | 1 (1 year) | — | — | — |
| 1925 | 2 | 1 | — | — | — | — | 1 |
| 1926 | 6 | 2 | 1 | — | 2 | — | 1 |
| 1927 | 3 | 2 | — | — | — | — | 1 |
| 1928 | 6 | 2 | 1 | 1 (3 years) | — | — | 2 |
| 1929 | 3 | 3 | — | — | — | — | — |
| 1930 | 4 | 2 | 1 | — | — | — | 1 |
| 1931 | 7 | 4 | 1 | 1 (5 years) | — | — | 1 |
| 1932 | 8 | 5 | 2 | — | — | — | 1 |
| 1933 | 9 | 4 | 2 | 1 (6 months) | — | 1 | 1 |
| 1934 | 9 | 6 | 1 | — | 1 (1 year later) | — | 1 |
| 1935 | 6 | 4 | 2 | — | — | — | — |
| 1936 | 12 | 11 | 1 | — | — | — | — |
| 1937 | 8 | 8 | — | — | — | — | — |
| Totals | 85 | 55 | 12 | 4 | 3 | 1 | 10 |

These observations are in agreement with those of Kjaergaard (1932), who followed up 49 patients and found that only one developed pulmonary tuberculosis subsequent to spontaneous pneumothorax. This patient was exposed to tuberculous infection in her home subsequently, and the two lesions were on opposite sides; it would hardly be proper, therefore, to associate the later tuberculosis with her attack of spontaneous pneumothorax. None of the other 48 patients showed any subsequent signs of pulmonary tuberculosis, yet most of them were under observation for a number of years:

| | | | |
|---------------------|---|--------------------|----|
| Over 15 years . . . | 2 | 5 to 8 years . . . | 9 |
| 10 to 15 „ . . . | 6 | 3 to 5 „ . . . | 25 |
| 8 to 10 „ . . . | 4 | 2 „ . . . | 2 |

Enneking's (1923) four cases showed no subsequent tuberculosis in 18, 16, 11, and 11 years respectively. Biesenthal and Snyder (1932) reported a series of 12 cases of spontaneous pneumothorax which they followed up for nine years and found no subsequent evidence of tuberculosis. In the literature only five cases have been found where pulmonary tuberculosis has developed following a pneumothorax of this type. These were recorded by Mosheim (1905), Hamman (1916), Kleeman (1918), Faschingbauer (1919), and Lindhagen (1919), and in no instance did the pulmonary tuberculosis occur within two years of the pneumothorax.

Thus, in a survey of the literature which includes about 250 recorded cases of benign spontaneous pneumothorax, it has been possible to find a record of only six developing chronic pulmonary tuberculosis. This is an incidence of 2 per cent. In the 85 cases occurring in the London Hospital in the last twelve years it has not been possible to find one case which subsequently developed that disease. It is, therefore, evident that the incidence of tuberculosis in patients who have had a spontaneous pneumothorax is no higher than in the general community. It would appear that the idea of a minimal subpleural tubercle as a cause of this type of pneumothorax is

entirely theoretical, and completely devoid of any backing either clinical or pathological.

2. *Rupture of an air vesicle on the surface of the lung.* (a) *Generalized emphysema.* In many treatises on medicine, generalized emphysema is regarded as the second most important cause of spontaneous pneumothorax, rupture of an emphysematous bulla being the immediate cause of the accident. It is easy to understand how the same atrophic processes which destroy the alveolar walls may occasionally spread and involve the visceral pleura. In those cases of benign spontaneous pneumothorax that recover, the recognition of emphysema must rest on clinical observations; and while it may be easy to diagnose gross emphysema in the elderly and to exclude its presence in the young, the two extremes merge imperceptibly into one another. Cabot states 'Whether there is any clinical picture, or any physical signs are recognizable as corresponding with this lesion I am quite uncertain. Till 1921 I thought I could recognize emphysema. The following facts have disillusioned me. In 12 cases diagnosed as emphysema at the Massachusetts General Hospital only three showed any emphysema at *post mortem*. On the other hand, of 153 cases demonstrated *post mortem* only seven were recognized in life. I know to-day nothing about the physical signs of emphysema.'

Generalized emphysema occurs in young people only as a complication of asthma. In asthma the intra-alveolar tension is at times high from spasm of the bronchiolar muscles. It might be expected that if spontaneous pneumothorax were frequently due to generalized emphysema it would commonly occur in cases of asthma. Yet in searching the literature it has been possible to find only five cases, Fraentzel (1877), Emerson (1923), Kahn (1923), Symes-Thompson (1930), and Casiello (1937). In the present series there is no case in which a spontaneous pneumothorax has arisen in a patient suffering from asthma. The majority of patients with benign spontaneous pneumothorax do not show any great degree of anoxaemia. Whereas a patient who already has his alveolar surface greatly reduced by generalized emphysema is likely to be rendered gravely ill with severe anoxaemia if this surface is further reduced by a super-added spontaneous pneumothorax. That this is so is shown by the results of spontaneous pneumothorax arising while attempts were being made to treat generalized emphysema by means of artificial pneumothorax, as advised by Ganter (1926), in cases reported by Wiele (1928), and Christie (1934). For the same reason spontaneous pneumothorax occurring in generalized emphysema should have a high mortality rate. Autopsies recording the combined condition should therefore be comparatively frequent, but in fact none have been recorded in the London Hospital in the period 1924 to 1937, and only 12 cases (De Villiers, 1826; Rheder, 1866; Fraentzel, 1875; Zahn (three cases), 1891; Pitt, 1900; Orth, 1905; Bach, 1911; Massini and Schönberg, 1916; Meyer, 1917; Emerson, 1923) have been reported in the literature. Christie (1934) has shown that cases of generalized hypertrophic emphysema have a typical

vital capacity tracing. This shows overstretching on deep inspiration with failure to return to the resting level for several breaths; there is a considerable difference in the volume of reserve air taken alone and taken at the end of a vital capacity test; and there is also an irregularity in the resting respiration level.

Evidence of Emphysema

| Age at time of pneumothorax. | Symptoms. | | | X-ray. | Vital capacity. | Combined probability. |
|------------------------------|----------------------|--------|--------|--------|-----------------|-----------------------|
| | Shortness of breath. | Cough. | Signs. | | | |
| 19 | o | o | o | + | Trace | + |
| 24 | o | o | o | o | Trace | ? |
| 24 | o | o | o | Trace | o | ? |
| 26 | o | o | o | + | o | ? |
| 26 | o | o | o | Trace | o | ? |
| 30 | o | o | o | Trace | o | ? |
| 36 | ++ | + | + | + | Not measured | + |
| 38 | o | o | o | + | o | ? |
| 39 | + | + | + | + | Trace | + |
| 41 | + | + | o | o | o | o |
| 42 | ++ | + | + | + | + | + |
| 42 | + | + | o | — | Not measured | ? |
| 42 | ++ | + | ++ | + | o | + |
| 43 | ++ | + | + | + | Trace | + |
| 43 | + | + | o | o | Trace | + |
| 43 | o | o | o | — | Not measured | o |
| 49 | o | o | o | + | o | ? |
| 49 | ++ | + | + | Trace | + | + |
| 49 | ++ | + | + | — | Not measured | + |
| 49 | o | o | o | Trace | Trace | + |
| 50 | + | + | o | o | No co-operation | ? |
| 51 | + | + | + | o | Not measured | ? |
| 56 | + | + | o | o | + | + |
| 56 | ++ | + | + | o | Trace | + |
| 57 | ++ | + | + | Trace | + | + |
| 58 | + | + | o | + | Trace | + |
| 60 | ++ | ++ | ++ | + | Not measured | + |
| 63 | ++ | ++ | ++ | Trace | + | + |
| 65 | ++ | + | ++ | + | Not measured | + |
| 66 | ++ | ++ | ++ | o | Not measured | + |
| 69 | + | + | o | — | Not measured | o |

An attempt has been made in the present series to determine how many patients suffered from generalized hypertrophic emphysema, (1) by clinical evidence, (2) by the independent unbiased opinion of a radiologist, Dr. L. J. Rae, on the evidence of emphysema in the radiograms, and (3) by vital capacity tracings.

The results of this investigation are set out in the table above. Only those patients under 40 years of age who showed some evidence in one section or another are included in the table. All patients over the age of 40 years are included. It is seen that in the group of patients over the age of 40 years, all except two show some evidence of generalized emphysema. The incidence of generalized emphysema in patients over 40 years who have suffered from benign spontaneous pneumothorax is therefore substantially

higher than the incidence in the general community. In the present series of 85 cases of benign spontaneous pneumothorax, it has been found that 18 suffered from generalized emphysema. The conclusion is that while in generalized emphysema an air vesicle may burst and give rise to a benign spontaneous pneumothorax, it is by no means the commonest cause of such a pneumothorax.

(b) *Localized emphysema and scar-tissue formation.* Many recent writers on this subject try to draw a distinction between localized emphysema, scar-tissue vesicles, and subpleural blebs. By the last term they imply that the pleura is split, producing a surgical emphysema in that covering, with the formation of a bleb. All three conditions are closely allied, and since so few patients with benign spontaneous pneumothorax die, there is not sufficient histological material available to differentiate them clearly, or to form any opinion as to which is the most frequent cause of benign spontaneous pneumothorax. In generalized emphysema there is always scar-tissue present in the lungs and pleura; it is possible therefore that when a spontaneous pneumothorax arises in such a patient it is caused by the rupture of a scar-tissue vesicle, and not by rupture of a hypertrophic emphysematous bulla. Similarly, it is possible for a localized emphysematous bulla to burst and produce a pneumothorax. Localized emphysema is a lesion which is found at all ages and gives rise to no symptoms. Patients with such a condition suffer from neither dyspnoea nor cardiac insufficiency, as do those with generalized emphysema; and therefore they can more readily survive a pneumothorax. The bursting of this type of vesicle is theoretically the most probable cause of benign spontaneous pneumothorax, and there is some histological material to support this theory. Ranking (1860) reported the case of a healthy man, aged 19 years, who developed a large left pneumothorax. Two months later, having completely recovered from this, he died with a dissecting aneurysm. At necropsy the left lung showed a few distended emphysematous vesicles near the apex, but no other abnormality.

Hayashi (1915) reported three cases:

1. A woman, aged 60 years, who had had a chronic pneumothorax died after an operation for carcinoma of the stomach. At necropsy there was a left-sided pneumothorax. On the surface of the left lung near the apex and next to an adhesion was a distended emphysematous vesicle, in which was a small round hole. The rest of the lung was anthracotic and showed no evidence of active tuberculosis.

2. A woman, aged 47 years, developed a tense left-sided pneumothorax and died. The pneumothorax was confirmed at necropsy, and at the apex of the left lung numerous emphysematous bullae were found, of which one was ruptured. In the lung parenchyma there was old healed fibrous tuberculosis.

3. A man, aged 19 years, developed bilateral pneumothorax and died. Necropsy confirmed the bilateral pneumothorax, and showed several groups of thin-walled emphysematous bullae in the left lung, one of which had

a small perforation. The right apex was fixed to the chest with cord-like adhesions, and next to these was a group of emphysematous bullae. There was no sign of tuberculosis, either macroscopic or microscopic.

Fischer (1922) reported the case of a man, aged 22 years, on whom laparotomy was performed for a mistaken diagnosis of perforated duodenal ulcer. Necropsy revealed a right-sided haemopneumothorax. There was no abnormality in the right lung, except several emphysematous vesicles at the apex; one of these showed a small rupture. Settle (1936) records the case of a boy of 15 years. Necropsy revealed a tense right pneumothorax and a ruptured emphysematous bulla in the right lung. Willcox and Foster-Carter (1937) described a left-sided pneumothorax in a man aged 35 years. Radiograms showed a large emphysematous bulla at the left base. The pneumothorax became very tense and the patient died. The presence of the emphysematous bulla was confirmed at necropsy. According to Orth (1905), and Fischer (1922), scar-tissue vesicles are formed through atrophy and inflation of portions of lung tissue resulting from the presence of a 'valve-like' structure at the base of the vesicle. The valve allows the air to pass freely into the vesicle, but acts as an obstruction to its return. This is proved by the fact that it is very difficult or impossible to force air out of these vesicles. The vesicle gradually increases in size, and finally the wall becomes so thin and atrophic that it ruptures. As to the origin of this scar-tissue Fischer suggests that it is usually due to a previous limited tuberculous affection, and that this accounts for these valvular vesicles usually being situated at the apex of the lung. Kjaergaard (1935) followed up this idea of Fischer and reports three autopsies in patients who died from other causes, but whose lung contained these valvular vesicles. In two cases the vesicles were due to scar-tissue, but in one case there was a valvular vesicle without scar-tissue, which he considered to be due to bullous emphysema. He then suggests that the infrequency of spontaneous pneumothorax in patients with generalized emphysema is due to the fact that emphysematous bullae are rarely valvular vesicles and as a rule communicate freely with the underlying lung tissue. Localized emphysema is a frequent sequel of many pathological conditions in the lung, and patients suffering from these conditions occasionally develop a spontaneous pneumothorax from rupture of an air vesicle; it is usual to ascribe these cases to the original condition, but autopsy shows that rupture of 'emphysematous bullae' is the immediate cause of pneumothorax. Saltzman (1926) gives the case of a patient who had a carcinoma of his left lung and died from an added pneumothorax on the same side. At autopsy the carcinoma was found surrounded on all sides by healthy lung, and the pneumothorax was caused by rupture of a superficial emphysematous bulla.

In three fatal cases in the present series, in which pneumothorax has occurred in patients with active tuberculosis, autopsy has shown the pneumothorax to be due to rupture of an emphysematous bulla and not to tuberculous ulceration. Further, in this series there have occurred six cases

in which radiograms have shown a healed tuberculous focus in the lung. These have not shown any activity either at the time of the pneumothorax or subsequently. In one case the patient was a radiographer at the London Hospital and has therefore been constantly under observation. It is interesting to find that Glickman and Schlomovitz (1936) have collected from the literature seven cases of simultaneous bilateral pneumothorax arising in connexion with pneumoconiosis. This is a condition characterized by multiple scars throughout the lung, and it is probable that scar-tissue vesicles were the cause of the pneumothorax here also. In the present series the only case of benign spontaneous pneumothorax which died showed at autopsy rupture of a bulla in a localized area of emphysema. A section of this bulla is shown in Plate 1, Fig. 3. An emphysematous bulla is seen complete, together with one beside it collapsed and showing a well-marked rent on the surface. This patient died from septicaemia following a whitlow, the spontaneous pneumothorax being an entirely independent occurrence. The nature of the scar which gave rise to these vesicles was quite unidentifiable. Since the invention of thoracoscopy it has been possible to see the bullae during life in patients with spontaneous pneumothorax, Wiele (1928) passed a thoracoscope in a case of pneumothorax in an apparently healthy man, aged 37, and though he was unable to see any rupture in the visceral pleura, he saw numerous emphysematous bullae up to the size of a cherry. In the case quoted by Staby (1935) a ruptured vesicle was actually seen. Professor R. V. Christie has shown me the notes of two patients with spontaneous pneumothorax on whom thoracoscopy was performed at the Royal Victoria Hospital, Montreal. In both of these cases he saw subpleural air-containing vesicles. In 1937 Castex and Mazzei published a paper in which there are two excellent coloured plates of these vesicles standing out on the surface of the lung. The authors do not record how many times they have performed thoracoscopy or how frequently they have seen these vesicles, but their plates are striking evidence of the existence of the vesicles. There is not an illustration of one ruptured, but it is easy to imagine how such an event might occur.

(c) *Congenital cysts of the lung.* Congenital cystic disease of the lung attracted little attention until Koontz (1925) published an account of 108 cases of congenital malformations of the lung which he had collected from the literature; of these cases about 50 per cent. showed some cystic change. The cysts vary greatly in regard to size, number and situation. It is stated that in the variety in which cysts appear on the surface of the lung, a cyst may rupture and give rise to a spontaneous pneumothorax. Folke (1935) gave a good résumé of the literature on persistent spontaneous pneumothorax in infants. He collected a series of 19 cases from the literature and added one of his own. The onset of all these cases was under the age of 4 months. There were nine deaths and seven autopsies with the following findings:

(1) Total left pneumothorax. Emphysematous vesicles. Tear in pleura 3 cm. in length.

- (2) Total left pneumothorax. Subcutaneous emphysema.
- (3) Total left pneumothorax.
- (4) Pencil-thick patent bronchus opening on the surface of the lung. Right total pneumothorax.
- (5) Total right and partial left pneumothorax. Emphysematous vesicles.
- (6) Bilateral pneumothorax. Emphysematous vesicles.
- (7) Total right pneumothorax. Multiple small cysts (anomaly of development).

This interesting series of cases suggests that spontaneous pneumothorax is more common in infants than has been generally recognized, and would be diagnosed more frequently if this possibility were considered. It also suggests that some 'emphysematous vesicles' may really be congenital in origin. Miller (1926) records three patients with congenital cystic disease of the lungs who had had recurrent attacks of dyspnoea and cyanosis. They were aged 5 weeks, 12 days, and 5 months respectively. In the first case radiograms showed a right-sided pneumothorax. The child died, but there was no autopsy. In the third case no X-rays were taken and there was therefore no conclusive evidence of pneumothorax, but autopsy revealed congenital cystic disease of the lungs. His conclusion that infantile pneumothorax was due to rupture of a congenital cyst is not proved, but that pneumothorax can occur at the age of 5 weeks is proved beyond doubt. Autopsies on patients aged 4, 22, and 28 years in which the authors for various reasons considered the pneumothorax due to a ruptured congenital cyst are reported by Orth (1905), Schmincke (1928) and Oeschli and Miles (1934). Kjaergaard (1933) published post-mortem examinations on two patients, aged 61 and 79 years, who died with a spontaneous pneumothorax. In each case the cause was found to be a ruptured 'valve vesicle' on the surface of the lung. In both of these patients there were 'bronchiectatic cysts' within the lungs; and in the first there was no middle lobe in the right lung. Because of these findings Kjaergaard considered these 'valve vesicles' to be congenital. It would seem, however, that necropsies in patients at the age of 79 and 61 years can hardly be regarded with confidence as evidence that the cysts were congenital; it seems more likely they were emphysematous bullae. These two cases are at least evidence of spontaneous pneumothorax arising from rupture of a vesicle on the surface of the lung. In recent years it has been claimed by many writers that clear round areas surrounded by ring shadows in radiographs of lungs are evidence of congenital cysts. There is no doubt that such areas can be seen and that they are due to air vesicles, but the only evidence that these vesicles are congenital would appear to be the author's opinion. Thus Kjaergaard (1933) showed these appearances in the lungs removed at autopsy in the two cases described above. The radiographs he reproduces show these air vesicles in an excellent manner, but offer no proof that they were necessarily congenital in origin. Cases of pneumothorax in which cysts have been demonstrated in radiograms and been assumed by the authors to be congenital in origin are

reported by Fleming (1934), Markson and Johnson (1934), Gordon (1936) and Castex and Mazzei (1937).

On reviewing this evidence, it is apparent that various authors claim for different reasons that air vesicles are congenital. Some claim incidence under the age of five years, some claim the presence of other congenital abnormalities, some claim that they are congenital because they are scattered throughout the lung, others because they are solitary, still others claim the recurrence of pneumothorax as evidence. It is possible that most vesicles in the lung are congenital and have been present from birth without causing symptoms. Conclusive proof on these points is not available, and therefore must await further research. The opinion that congenital cystic disease of the kidney is congenital is based to a large extent on its transmission through families as a Mendelian dominant. This evidence is lacking in spontaneous pneumothorax, as so few cases of familial incidence are reported that they are most probably due to coincidence.

3. *Pleural adhesions.* Pleural adhesions are sometimes regarded as evidence of pulmonary tuberculosis, but they may be the sequel of any form of pleurisy. They have been suspected of causing spontaneous pneumothorax. It is said that they cause the formation of fragile subpleural air vesicles at the point of their insertion to the visceral pleura, and that during a violent respiratory effort they pull on the lung and tear these vesicles. Such an occurrence is well illustrated by the autopsies recorded by Pitt (1900), Brunner (1921), Housden and Piggot (1931), and Gough (1937). When a pleural adhesion of sufficient size to cause a tear in the lung is ruptured it will almost certainly bleed and give rise to a haemopneumothorax. In the cases of Pitt, and of Housden and Piggot the haemorrhage was severe enough to cause the death of the patient. Since most cases of benign spontaneous pneumothorax contain at the most a few drachms of fluid, and that discernable only in radiograms, it is unlikely that ruptured adhesions are a common cause of the condition.

4. *Effort.* The opinion of most authors on this subject is that effort plays an important part in precipitating spontaneous pneumothorax. Friesdorf (1927) in a series of 177 cases collected from the literature found that 40 per cent. arose after considerable exertion, 40 per cent. after slight exertion, 20 per cent. after trivial movements. No great value can be attached to these figures since the information collected is second-hand from the literature and the degree of exertion difficult to assess, but they do at least suggest that pneumothorax may occur independently of excessive exertion. West in 1884 showed that a rupture of the pleura could not be produced by inflation of normal lungs removed *post mortem* until the pressure was above 200 mm. of mercury. He further pointed out that such a great intrapulmonary pressure can never arise in life and therefore rupture cannot be brought about simply by coughing or muscular exertion. There must be some additional pathological condition weakening the pleura where it ruptures.

The possibility of a sudden effort tearing a healthy pleura is also denied by Diez (1929). He said that though it was generally thought that the intra-alveolar pressure rose during effort when the glottis was closed and chest muscles contracted, Pierracini had demonstrated that in reality it remained constant and that it increased only in movements which forcibly reduced the size of the chest. Even then the rise was not sufficient to be capable of overcoming the elastic recoil of a normal lung.

If effort played an important part in the production of benign pneumothorax, the condition would be expected to occur with greater frequency in those persons who are employed in strenuous manual labour than in persons who do light work, or sedentary work. Both in this series and in that recorded by Kjaergaard no such difference can be established. It occurs in all types of workers with equal frequency. Kjaergaard (1932) found the occupation of his patients as follows:

| | |
|---|----|
| Heavy physical work (blacksmith, farmer, baker, &c.) | 13 |
| Household work (housewife, servant) | 10 |
| Less exhausting physical work (electrician, shoemaker, &c.) | 8 |
| Shop clerks, functionaries, agents | 6 |
| Office workers | 7 |
| Students | 6 |

In the present series the occupation of the patients was:

| | |
|---|--------|
| Clerks | 12 |
| Tailors | 10 |
| House duties and labourers | 6 |
| Children | 4 |
| French polishers and drivers of public service vehicles | 3 each |
| Pressers, furriers, machinists, cabinet makers, railway checkers, medical students, and retired men | 2 each |
| Other occupations (33) | 1 each |
| Total | 85 |

If effort does not play the principal part in producing a spontaneous pneumothorax it is possible that it plays a contributory part in precipitating a phenomenon which has been facilitated by long-standing alterations in the pleura. Wilson (1926) suggests that effort may act indirectly by causing larger respiratory movements with greater movement between the visceral and parietal pleura; these, he states, may favour the tearing of pleural adhesions. However, as pleural adhesions are not a frequent cause of pneumothorax, this statement, as it stands, is of little importance. It is a striking fact that in 30 cases, 35 per cent. of the present series, the patient was seized with a sudden pain either on getting out of bed in the morning or while washing in the morning, or on walking to work in the morning. Three cases have followed anaesthesia, and other cases have occurred in patients while leaving a cinema. These facts suggest that respiratory movements of greater amplitude following a period of shallow respiration, such as sleep, may play a part in precipitating the onset of a benign spontaneous pneumothorax. It is probable also that awkward posture plays a part; when the trunk is bent to one side the lung on the

same side must be compressed while the lung on the opposite side is stretched.

Summary of Aetiology of Benign Spontaneous Pneumothorax

It appears, therefore, that though pneumothorax may occur in the course of known pulmonary tuberculosis, yet pulmonary tuberculosis is not a cause of pneumothorax in the apparently healthy. Similarly, ruptured adhesions are shown to give rise to haemothorax or haemopneumothorax rather than to benign pneumothorax. Trauma is seen to play at most a small contributory role and therefore it is apparent that benign spontaneous pneumothorax must usually arise from the rupture of a subpleural air vesicle, either of emphysematous, scar tissue or congenital origin. Direct pathological evidence in support of this view has been obtained in a few cases.

Incidence

Benign spontaneous pneumothorax is a comparatively rare disease, and this accounts for the fact that the only series of over 50 cases personally collected is that published by Kjaergaard (1932). Kjaergaard's 51 patients appeared in fifty hospitals in Denmark over a period of twenty years. The yearly incidence in the London Hospital (recurrent cases counted on the first occasion only), has been :

| | | | | | | | | | |
|-------|---|---|---|---|------|---|---|---|----|
| 1924 | . | . | . | 2 | 1931 | . | . | . | 7 |
| 1925 | . | . | . | 2 | 1932 | . | . | . | 8 |
| 1926 | . | . | . | 6 | 1933 | . | . | . | 9 |
| 1927 | . | . | . | 3 | 1934 | . | . | . | 9 |
| 1928 | . | . | . | 6 | 1935 | . | . | . | 6 |
| 1929 | . | . | . | 3 | 1936 | . | . | . | 12 |
| 1930 | . | . | . | 4 | 1937 | . | . | . | 8 |
| Total | | | | | | | | | 85 |

There are about 10,000 admissions to the hospital annually. The increase in numbers in the last seven years may be assigned to the more general use of radiology in patients who attend hospital with pains in the chest.

Sex and age incidence. Since West in 1884 communicated a series of 21 cases (19 males and two females) to the Clinical Society of London it has been established that benign spontaneous pneumothorax occurs at least five times as commonly in males as in females. The following series of cases, collected from the literature, have been published and confirm this fact.

| | Males. | Females. |
|-----------------|--------|----------|
| West (1884) | 19 | 2 |
| Galliard (1888) | 19 | 3 |
| Enneking (1923) | 123 | 26 |

More recently, the following groups of personally observed cases are available :

| | Males. | Females. |
|-----------------------------------|--------|----------|
| Olbrechts (1930) | 9 | 2 |
| Kjaergaard (1932) | 36 | 15 |
| Leggett, Myers, and Levine (1934) | 17 | 2 |
| The present series | 78 | 7 |

From a survey of the ages of the patients in the longest of these series and in the present series, it is evident that benign spontaneous pneumothorax occurs most commonly between the ages of 15 and 35 years. No age, however, is exempt.

| | Enneking. | Olbrechts. | Kjaergaard. | Biesenthal and Snyder. | Castex and Mazzei. | The present series. |
|-----------------|-----------|------------|-------------|------------------------------|--------------------------|---------------------------|
| Under 10 | 8 | 2 | 1 | 0 | 0 | 3 |
| 10-20 | 29 | 2 | 5 | 4 | 0 | 11 |
| 20-30 | 48 | 6 | 22 | 2 | 9 | 33 |
| 30-40 | 19 | 1 | 14 | 4 | 3 | 16 |
| 40-50 | 17 | 0 | 9 | 2 | 0 | 11 |
| 50-60 | 9 | 0 | 0 | 0 | 0 | 7 |
| Over 60 | 1 | 0 | 0 | 0 | 0 | 4 |
| Stated young | 19 | | | | | |
| Stated old | 1 | | | | | |

Localization. The incidence on the two sides appears to be about equal, and is as follows:

| | Enneking. | Olbrechts. | Kjaergaard. | The present series. |
|----------------------------------|-----------|------------|-------------|---------------------|
| Right side | 73 | 4 | 33 | 35 |
| Left side | 66 | 7 | 17 | 48 |
| First one side then the other | 3 | 0 | 1 | 2 |

Clinical Features

A patient with a spontaneous pneumothorax most often comes to hospital complaining of a pain in some part of his chest, usually the side on which the accident has occurred. This pain is of sudden onset so that the patient gives the exact moment it occurred and what he was doing at the time; on the other hand, more rarely, the onset may be extremely gradual with the patient unable to date it at all. Sometimes the pain is situated in the shoulder or the back, and rarely the patient complains of pain in the upper abdomen. Burrell states that he has seen a case of spontaneous pneumothorax mistaken for a perforated gastric ulcer, and the case described by Gough (1937) had a laparotomy for the same mistaken diagnosis. Oeschli and Skillen (1933) and Settle (1936) also quote cases in which the disease started with upper abdominal pain. It is probable that this abdominal pain is caused by irritation of the diaphragmatic pleura with blood, and this would explain why it is nearly always present and severe in cases of spontaneous haemothorax. The pain is generally followed by shortness of breath especially on exertion, and sometimes the patient may be cyanosed. After pain, the most common initial symptom is dyspnoea. When present as an initial symptom the dyspnoea is a reflex phenomenon and superficial, due to shock, and is not to be mistaken for that which subsequently occurs in the majority of cases.

Cyanosis is rarely marked, and this is not surprising. Christie and McIntosh (1936) point out that it has been established, by estimating the

oxygen in arterial blood, that though immediately after collapse of the lung there is some anoxaemia, it is only transient. This is explained by the fact that immediately the lung collapses the pulmonary arterial supply ceases, leaving only the bronchial supply; further, the arterial supply to the other lung is greatly increased, thus keeping the blood oxygenated and explaining the congestion of the contralateral lung always seen in radiographs.

Among the less common initial symptoms, haemoptysis is perhaps the most usual, a little blood-stained mucus being coughed up, probably arising from the lung at the point of rupture. Haemoptysis was the first symptom in three cases in this series, and Kjaergaard reports two similar cases. Szenes (1928) reports a case with a large haemoptysis, but this is a rare occurrence. When a haemopneumothorax results from a torn pleural adhesion, the initial symptoms may be faintness and pallor, followed by collapse. Vomiting may occasionally occur as an early symptom, and Kjaergaard (1935) reports one case in which the lesion was ushered in by hiccough. In a few cases the patient is greatly shocked by the accident, and this is largely dependent on the amount of air, and the rapidity with which it is drawn into the pleural cavity.

The physical signs will depend to a large extent on the amount of air in the pleural cavity. They are: diminished movement of that side of the chest, diminished tactile vocal fremitus, hyper-resonance, diminished or absent breath sounds, and in some cases the coin sound. It is worthy of record that the last sign was present in only 17 cases in this series of 85. If the amount of air in the pleura is small, the heart and trachea are not likely to be appreciably displaced, but all degrees of displacement may occur. Thus in a left-sided pneumothorax the trachea may lie under the right sternomastoid muscle and the apex-beat be found to the right of the sternum. When this occurs the patient is liable to be greatly distressed, cyanosed, and orthopnoeic. In these cases there is a rise of temperature and the pulse-rate is rapid, both of which are immediately relieved by removal of the air (Fig. 1). From what has been said it is clear that it is often difficult to diagnose spontaneous pneumothorax on the history and physical signs alone. These may be vague and equivocal, and diagnosis can be established conclusively only by an X-ray examination. This investigation should be carried out in all patients who complain of a pain in the chest. The congestion of the opposite lung from increased blood supply, which is always present to some degree, should not be mistaken for tuberculous infiltration.

Diagnosis

This is difficult unless the possibility of pneumothorax is kept in mind. The site of the pain is frequently misleading, and a patient who comes to hospital complaining of pain in the shoulder or back is easily labelled

'rheumatism', 'fibrositis', or 'lumbago'. When the pain is in the chest the condition may be labelled 'pleurisy'. In cases where there is a displacement of the mediastinum the diagnosis is easy, because in these cases the other signs are well marked. It may be difficult to differentiate even

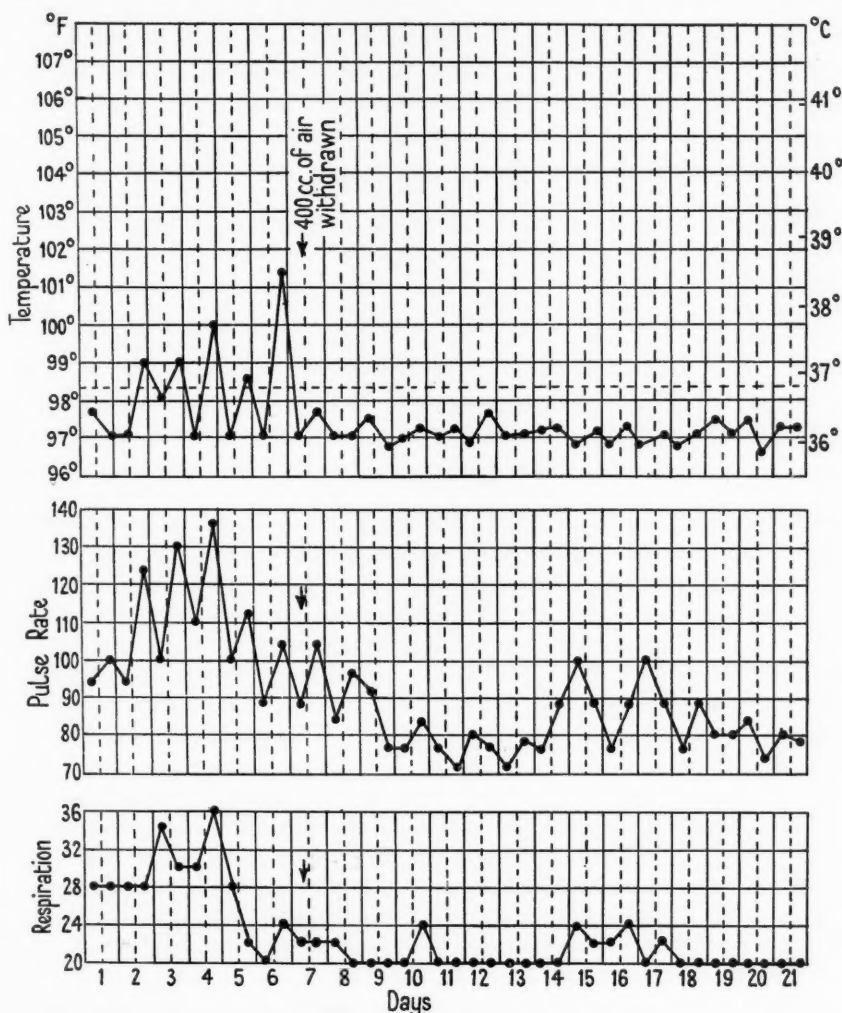


FIG. 1.

radiologically a case of spontaneous pneumothorax from one with a very large emphysematous bulla; the size to which such a bulla may grow is shown by the illustration of the X-ray taken of one case in the present series when he attended for his follow-up examination (Plate 2, Fig. 4). A diaphragmatic hernia may give physical signs and radiographic appearances superficially resembling a spontaneous pneumothorax, but with care the

conditions should not be confused. A large subphrenic abscess containing gas is also capable of being confused with a spontaneous pneumothorax. In cases of bilateral spontaneous pneumothorax it is not possible to compare the signs on the two sides, but the patient is usually very ill, and there is no fear of the condition being lightly regarded and therefore missed. In relapsing or alternating pneumothorax the diagnosis is not so difficult as in the first attack, and often the patient makes the diagnosis himself as soon as the same symptoms reappear.

Course and Prognosis

The course of spontaneous pneumothorax is favourable in the majority of cases. In this series of 85 there was only one death, due to a concurrent septicaemia following a whitlow. This low mortality-rate is also borne out by the few autopsies which it has been possible to find in the literature. The forms of the disease which involve a danger to life are: 1. tense pneumothorax, 2. haemopneumothorax, 3. bilateral pneumothorax.

In a survey of the literature it has been possible to find 21 cases of haemopneumothorax, of which eight have died, a mortality-rate of 37 per cent.; and in 20 cases of bilateral pneumothorax 10 have died, a mortality-rate of 50 per cent. In most cases in this series, where records are available, it has been found that the lung has expanded before the patient has left hospital in four to six weeks. Further, in only two cases has a pneumothorax been present at the follow-up examination. In one case the pneumothorax lasted for twenty years, and in the other the pneumothorax was still present after four years. This radiograph is recorded, since it is interesting to note that the pleura is calcified (Plate 2, Fig. 5). Both these patients were fit enough to carry on with their normal life, and suffered from extremely little dyspnoea considering their condition. In this connexion, Hirschboeck (1930) reported the case of a man of 41 who had a chronic pneumothorax with calcified pleura for eleven years and yet was able to work at manual labour.

This is in accordance with the findings in the literature. Fishberg states that Nikolski found that in 57 cases the air was absorbed in less than two months. Kjaergaard (1932) in his series of 51 cases found the lung expanded within three months in 46 instances. Of the other five, one took eight months, two took two years, one six years, and in one instance the lung was not re-expanded after twenty years. In exceptional cases, however, the pneumothorax persists for months or even years. Such cases have been reported by Olbrechts (1930), 3 years, Adams (1886), 7 years, Fishberg (1932), 8 years, Le Wald (1926), 11 years, Tideström (1924), 16 years, Levy (1918), 20 years, Wiele (1928), 21 years, and Bittorf (1908), 25 years. In the long-standing cases the problem arises as to how the air gets into the pleural cavity. Experience with artificial pneumothorax has shown that unless refills are made regularly the air is quickly absorbed, and it is considered exceptional when the lung does not re-expand after the cessation of refills.

It must be assumed, therefore, that in these chronic cases there exists a pleuro-pulmonary fistula which permits air from the lung to enter the pleural cavity. In nearly all cases the lung finally re-expands, so that the fistula must close eventually. A remarkable point is that, despite its persistence, there is rarely any infection of the pleural cavity. There is rarely any pleural effusion, and if there is, it is always serous and small in amount.

There are 33 single cases of recurrent pneumothorax recorded in the literature. This suggests that pneumothorax in the apparently healthy has a definite tendency to recur. It is impossible to say whether the recurrence is from the rupture of the same vesicle or of another. Nikolski, in his series of 90 cases, quotes nine instances of recurrent pneumothorax. In Kjaergaard's (1932) series of 51 patients, seven had recurring attacks, a recurrence-rate of 14 per cent.; and Wood (1931) states that in 71 patients at the Mayo Clinic, 21 per cent. gave a history of multiple attacks, and in 11 per cent. both a right-sided and left-sided pneumothorax had occurred at different times.

In the present series there are only four cases of recurrent spontaneous pneumothorax, a recurrence-rate of 4.7 per cent. This is much lower than Nikolski's figure of 10 per cent., which is not surprising since recurrent cases tend to be considered more worthy of publication than simple cases, and his figures were collected from the literature; but it is strange that they should be so much lower than the figures of 14 per cent. given by Kjaergaard and 21 per cent. given by Wood: for this there is no satisfactory explanation. Of the cases reported in the literature, the first relapse occurred within a year in 19 instances, and further, in only six did the first relapse occur after five years. In the four cases in the present series, the recurrence occurred after two days, two, eight, and ten years respectively. In the last three cases there was only one relapse, but in the first case there were at least eight known recurrences. From the literature it has been possible to find five cases which had three attacks, three cases with four, and four cases with more than five attacks. From the 'follow-up' of this series of patients it is evident that apart from these considerations, once the lung has expanded the patients have no disability and are no more prone to subsequent disease than normal persons.

Treatment

Since spontaneous pneumothorax in the apparently healthy is due to rupture of an air vesicle on the surface of the lung, it is evident that the condition cannot be prevented. In the mild cases, the patient frequently does not seek advice immediately, and when he does no treatment is required; in more severe attacks, rest in bed for one week should be sufficient to allow the perforation to heal. Sanatorium treatment is quite unnecessary. The patient should be warned that there is a certain relapse-rate, and that this is highest during the first year after the pneumothorax.

Tense pneumothorax usually develops slowly, though sometimes as an exacerbation two or three days after the onset of the original pneumothorax. The patient is greatly distressed, orthopnoeic, and cyanosed; the mediastinum is displaced and there is usually fever. Here aspiration is essential, and the result in these cases is striking. The temperature-, pulse-, and respiratory-rate immediately settle (Fig. 1). At the same time the anxiety and pain subside, the cyanosis disappears, and the mediastinum resumes its normal position.

Pneumothorax in severe generalized emphysema, or bilateral pneumothorax. Here the outlook is grave, since the area of lung tissue from which the blood can be oxygenated is dangerously reduced. Immediate removal of as much air as possible by means of an artificial pneumothorax apparatus is essential; in the case of bilateral pneumothorax it should be removed from both sides. Administration of oxygen by means of a bilateral nasal catheter, nasal mask, or oxygen tent is also valuable.

Recurrent pneumothorax. Relapses are treated on the usual principles, and patients should be advised to avoid severe exertion during the first year after a relapse, as the possibility of further relapses must be considered. No satisfactory method of producing uniform adhesions in the pleural cavity has yet been found.

Spontaneous haemopneumothorax presents a serious risk to the life of the patient from haemorrhage, and blood-transfusion, therefore, is of great value. It is also advisable to remove by aspiration the blood which has collected in the pleural cavity, and this must be done early before blood clot has formed.

Summary

1. Spontaneous pneumothorax has recently attracted increasing interest since routine radiography of the chest has made its diagnosis both easy and certain.

2. In 114 cases collected from the records of the London Hospital in the years 1924 to 1937 there were 16 cases of pneumothorax complicating pulmonary tuberculosis, 13 cases arising from other pulmonary diseases and wounds of the chest wall, whereas 85 (70 per cent.) occurred in previously healthy subjects with no apparent cause.

3. On analysis, the 15 tuberculous patients were found all to have developed a hydropneumothorax or a pyopneumothorax, and all ran a febrile course. The mortality-rate was over 50 per cent. within the first month. On the other hand, the 85 cases, occurring spontaneously in the apparently healthy, constitute a group which is distinct both clinically and pathologically. Clinically they are afebrile and never develop any effusion. More important, however, is the benign course which they pursue. Only two out of the 85 died while in hospital, and a 'follow-up' in 67 of the remainder showed that 28 were alive and well more than five years after the onset of the pneumothorax, and 26 more after periods between two and five years. In no case had active

pulmonary tuberculosis developed following a pneumothorax in the apparently healthy. It is therefore justifiable to use the term 'Benign Spontaneous Pneumothorax' to describe this condition.

4. There are, however, complications of benign spontaneous pneumothorax, and though the majority of cases make an uninterrupted recovery, the pneumothorax recurs in 4.4 per cent. Occasionally the pressure of the air in the pneumothorax rises so much that it causes great displacement of the mediastinum, and distress. This tense pneumothorax developed in three patients only, and was readily relieved by aspiration of the air. More serious complications are recorded in the literature. Accounts have been found of 20 cases of simultaneous bilateral pneumothorax, of which 10 were fatal, and 21 cases of spontaneous haemopneumothorax, of which eight were fatal. These are the immediate risks, and it is clear that in benign spontaneous pneumothorax expectant treatment is all that is usually needed. A favourable prognosis can be given, though there is a small risk of recurrence.

5. The etiology and pathology of the common benign form is still a subject of controversy. Active tuberculosis is certainly not responsible, because neither at the time of the attack nor in subsequent years can any evidence be found clinically or radiologically to suggest tuberculosis. The few cases that come to autopsy also reveal no active tuberculosis. Generalized emphysema is at most only an occasional factor. The majority of cases occur in patients below the age of 40 years, when generalized emphysema is uncommon; and subsequently when the pneumothorax has been absorbed no evidence of emphysema can be found by clinical methods, radiology, or vital capacity tests. The majority of recorded autopsies on spontaneous pneumothorax show no generalized emphysema. Ruptured adhesions cause a haemopneumothorax, and it is doubtful if they ever lead to a dry pneumothorax.

6. The immediate cause of a spontaneous pneumothorax is probably always rupture of an air-containing vesicle into the pleural cavity. This is occasionally actually seen at autopsy, though the rupture is often missed even when the vesicles are found. Sometimes in cases that do not die these vesicles have been seen radiologically or through a thoracoscope. The nature of these vesicles is discussed. They are said to be due either to congenital defect, to fibrous valvular obliteration of the smaller bronchi, or to localized emphysema. There does not seem sufficient evidence to decide at present which of these is the most important cause.

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Fig. 2. Radiograph of a child aged 4 years who developed right-sided spontaneous pneumothorax during an attack of whooping cough



Fig. 3. Photomicrograph ($\times 7$) of ruptured emphysematous bulla



FIG. 5. Radiograph showing calcification of the pleura in a case of chronic pneumothorax



FIG. 4. Radiograph showing very large emphysematous bulla at the apex of the right lung

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INSULIN RESISTANCE AND THE DIAGNOSIS OF THYROID DISEASE¹

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DIAGNOSIS of well-developed thyrotoxicosis presents little difficulty to the clinician, but this can hardly be said of those apparently milder forms of thyroid disease, in which the subjective symptoms are almost as marked as in the frank case, but in which the clinical signs are indeterminate, and the laboratory findings, with the methods at present available, negative. In such cases, which are far from being few in number, the tendency has been to postpone treatment and to wait for the development of more pronounced signs of thyrotoxicosis; during this time not only is the patient unable to lead a normal life, but his condition may suffer gradual deterioration. A plea for earlier recognition and treatment of these 'latent' forms of thyroid disease has recently been made by McEwan (1938). It may hopefully be anticipated that any method which will enable us to discern in abnormal thyroid function the cause of the symptoms in these obscure cases will be the means of preventing much ill health.

The multiplicity of the disturbances which are associated with abnormal thyroid function is one of the main reasons for the difficulties which attend the diagnosis of these less obvious forms of thyroid disease. It must be remembered that the work of the thyroid is not confined to the regulation of the rate of metabolism in the body, although this is a very important function; directly or indirectly the cardiovascular and nervous systems, the gastro-intestinal tract, metabolic processes such as those concerned with carbohydrate and protein, and other members of the endocrine system come under its influence. When the function of the thyroid is deranged, either because of this or of concomitant disturbances in other parts of the body, these various systems are affected, not uniformly, but in varying degree. For this reason to confine our investigations to any one feature, such as the metabolic rate, is to run the risk of forming a false idea of the function of the gland. The diagnostic difficulties are increased by the circumstance that the psychic disturbances which are so commonly associated with thyroid disease are also manifested in conditions which do not appear to bear any relation to the thyroid.

At the present time the B.M.R. is the most widely used criterion of thyroid function. If in a patient suspected to be suffering from thyroid

¹ Received August 30, 1938.

disorder the B.M.R. is found to be within normal limits, there is a temptation to exclude the thyroid as a possible cause of the symptoms, and to fall back upon a diagnosis of 'anxiety state'. Changes in the size of the thyroid do not afford much help in this connexion, since if the B.M.R. is normal there is no established method of determining whether or not the gland is responsible for the symptoms. Attempts have been made to overcome these difficulties, and determination of the circulation time (Goldberg, 1938), the Lugol response (Means, 1937), and the tolerance to creatine (Richardson and Shorr, 1935; Thorn, 1936; Sohval, King, and Reiner, 1938) have been advocated as more delicate methods for the detection of aberrations in the function of the thyroid.

It is the purpose of this paper to describe an abnormality of carbohydrate metabolism in thyroid disease which can be detected even in the absence of any significant increase in the B.M.R. This abnormality takes the form of a diminution in the sensitivity of the muscles to insulin. Thus we find that, whereas in the normal subject the rate at which the muscles withdraw sugar from the blood is greatly increased by insulin, this effect is either diminished or abolished in thyrotoxic and in many non-thyrotoxic cases of goitre.

Material and Methods

Our conclusions are drawn from a study of 35 cases of thyroid disease. For the sake of simplicity we have divided these cases into two groups on the basis of the height of the B.M.R. on admission to hospital. Thus we have put those in which the B.M.R. was greater than the upper normal limit of +15 per cent. into one group, and those in which the metabolism was within the normal limits into the other. We shall refer to the first group as *toxic* and to the second as *non-toxic* goitre, reserving the term *toxic* for those patients in whom the B.M.R. was raised.

The groups are made up as follows:

1. *Toxic goitre.* Five males and 12 females, of whom 11 were studied before and after sub-total thyroidectomy. These cases belong to a well-recognized clinical group in which the prominent symptoms are tachycardia, exophthalmos, tremor, nervousness, tendency to loss of weight, &c., associated with an increased metabolic rate. No useful purpose would be served by attempting further to divide these into primary and secondary forms of thyrotoxicosis since according to Dunhill (1929), Fraser (1931) and others these forms represent not disease entities, but merely different phases in the same toxic condition which merge one into the other; our present work affords no indication of any metabolic difference between them. The ages ranged from 21 to 69 years, the majority occurring in the third and fifth decades. None had been treated with iodine.

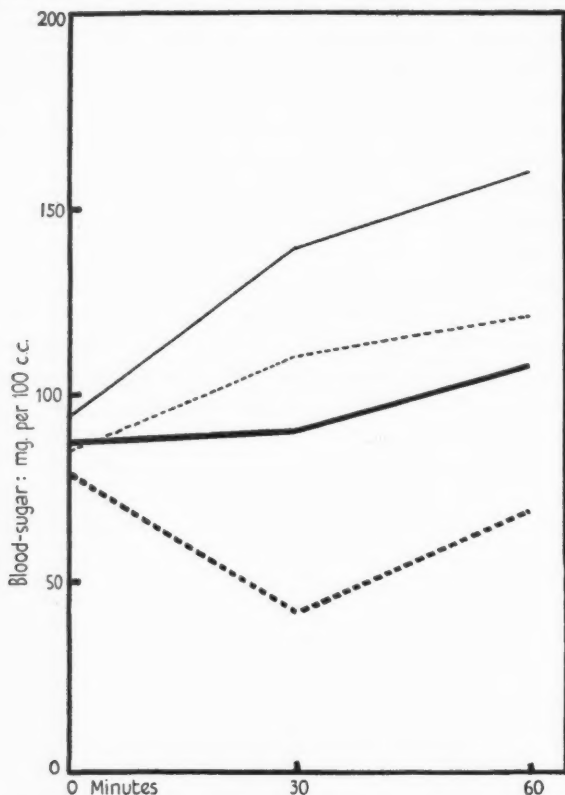
2. *Non-toxic goitre.* Four males and 14 females, of whom four were studied before and after sub-total thyroidectomy. In all cases the thyroid

was enlarged and the symptoms were similar to those of the first group, with the exception that persistent tachycardia was absent; eye signs were much less frequent. Easily produced fatigue was a pronounced symptom in 70 per cent., nervousness in 60 per cent., while the incidence of increased irritability was high. The severity of any given symptom varied from patient to patient and it was rare to find all the symptoms equally well developed. The ages ranged from 22 to 55 years; more than half fell in the fourth decade. Thus the incidence of this type of the disease, so far as can be judged from a small series, is greatest in the decade which lies between those in which the toxic state is most prevalent. Two only had received iodine, but not during the two months previous to investigation.

Methods. During absorption of sugar from the intestine the blood-sugar is under the control of insulin secreted from the pancreas in response to the rising blood-sugar level. Insulin exerts this control in two ways: (1) by promoting removal of sugar from the blood by the muscles and, (2) by checking the flow of sugar from the liver when the muscle stores are full. The first of these is termed the peripheral and the second the central action of insulin, and by their combined efforts the blood-sugar level is kept within the normal limits. The intensity of the peripheral action of insulin is indicated, as Foster (1923) showed, by the difference between the sugar concentrations in the arterial and venous blood supply of a limb, such as the forearm, which is referred to as the arteriovenous sugar difference (*a-v* difference); the central effect, as we have shown (Griffiths, 1938), by the course of the arterial blood-sugar. Thus the potency of the peripheral action of insulin is proportional to the *a-v* difference, and that of the central action is inversely proportional to the change in the arterial blood-sugar with respect to the initial value. These effects, the peripheral and the central, may be determined in one experiment by injecting insulin immediately before a dose of glucose by mouth and observing the subsequent changes in the arterial and venous blood-sugar; this is referred to as the *insulin-glucose test* and is based upon Himsworth's (1936) method.

The test. The patient is confined to bed and receives no food after supper on the eve of the test. After removing samples of blood for determination of the fasting blood-sugar, 5 units of insulin (Wellcome, prepared from crystalline insulin) are injected intravenously. Immediately after the injection of insulin the subject is given 50 gm. of glucose in 100 c.c. of water to drink. Further samples of arterial and venous blood are withdrawn thirty and sixty minutes after injection of the insulin, and the sugar in them determined. Arterial blood is obtained by *deep* puncture (3 mm.) of the pulp of the thumb or finger with a spring lancet. The first drop of blood is wiped away and a 0.2 c.c. pipette filled as the blood issues from the wound. The hand should be warm, and in order to maintain as far as possible uniform conditions and to ensure minimum muscular activity, the patient is instructed to keep the arm from which blood is to be taken under the bed-clothes and close to the body during the intervals between bleeding. Usually

the blood is obtained without difficulty, but sometimes gentle massage is necessary; a tourniquet must not be used. Immediately the arterial sample is obtained the venous blood must be drawn. The skin is sterilized with ether, a tourniquet applied to the arm, and without delay an antecubital vein is pierced with a fine needle attached to a small syringe and not more



Mean arteriovenous blood-sugar curves of a group of normal subjects to show the effect of injected insulin. Continuous lines = arterial blood-sugar. Dotted lines = venous blood-sugar. Thin lines = glucose alone. Thick lines = glucose + insulin.

than 0.3 c.c. of blood withdrawn. The blood is immediately transferred to a small tube from which 0.2 c.c. is taken up in a pipette before clotting occurs; no anti-coagulant is necessary. The same vein should be used throughout. It is both unnecessary and undesirable that the patient should open and close the hand, or clench the fist, during the process. Since the entire operation occupies less than a minute, the arterial and venous bloods may be regarded as being comparable. Blood-sugar was determined by MacLean's method and basal metabolism by the Douglas bag. If the B.M.R. is required, it may conveniently be determined before the insulin-glucose test. All the patients were taking a full diet.

The mean values for the arterial and venous blood-sugars in 13 normal persons subjected to the test are plotted in Fig. 1, together with those which would have been obtained after glucose alone. In the fasting state the arterial and venous blood-sugars are sometimes identical, but more frequently there is a variable difference which averages about 10 mg. per 100 c.c. of blood. It will be observed that when glucose alone is given the *a-v* difference is marked after thirty minutes, and that when one hour has elapsed the difference is even greater. This *a-v* difference is brought about by an increase in the rate at which the muscles remove sugar from the blood passing through them owing to the stimulus of insulin secreted by the pancreas in response to the rising blood-sugar level. When insulin is injected there is a similar increase in the *a-v* difference. Under these conditions the rise in the arterial blood-sugar is much smaller than when the insulin is derived from the pancreas; this is because in the latter case not only, in all probability, the amount of insulin, but also the mode of its entry into the circulation is different, whereas injected insulin is able immediately to exert its full force. For reasons that have been stated elsewhere (Griffiths, 1938) and which, as will be seen later, are substantiated by the present work, we believe this depression of the arterial blood-sugar to be due to the effect of the circulating insulin on the liver, causing it to store more of the incoming sugar from the intestine, and thereby reducing the amount passing into the blood-stream.

As will be learned from what follows, it is with respect to these effects of insulin on the central storage of sugar, and, more particularly, on the rate of its uptake by the muscles, that patients with thyroid disease show characteristic abnormalities. In expressing our results we have found it convenient to employ the following conventions: the *insulin-glucose response*, which is a measure of the central, or hepatic, sensitivity to insulin, is expressed as the algebraic sum of the differences between the initial arterial blood-sugar and the arterial blood-sugars thirty and sixty minutes after insulin injection; the *a-v index*, expressing the peripheral sensitivity, is the algebraic sum of the *a-v* differences at the above-mentioned times. Thus in the case of the following figures: arterial blood-sugar, 0.100, 0.095, and 0.115 per cent.; venous blood-sugar, 0.095, 0.072, and 0.101 per cent., the insulin-glucose response would be +10, and the *a-v* index +37. Small negative *a-v* differences (a negative difference exists when the venous blood-sugar is higher than the corresponding arterial value) are occasionally obtained in normal subjects. In thyroid disease we have encountered small negative differences a little more frequently than in normals, but to nothing like the same extent, either as regards number or magnitude, as in diabetes (Griffiths, 1938). When in the aggregate such negative differences predominate, the *a-v* index will have a negative value, indicating that in the main the venous blood-sugar was higher than the arterial throughout the test.

In the normal subject the *a-v* index varies within wide limits, thus in 13 cases the extremes were +26 and +170, with a mean value of +83.

In 18 normals the insulin-glucose response varied from -17 to $+70$, with a mean value of $+19$. Thus resistance to insulin in the peripheral tissues is indicated by an $a-v$ index of less than $+25$, and central resistance by an insulin-glucose response of more than $+70$.

TABLE I

Toxic Goitre.

| Case. | Sex. | Age. | B.M.R. %. | $a-v$ index. | Insulin-glucose response. | Creatinuria. |
|-------|------|------|-----------|--------------|---------------------------|--------------|
| G. H. | M | 23 | +50 | + 8 | + 32 | + |
| D. W. | F | 42 | +39 | +11 | +165 | + |
| A. T. | F | 37 | +70 | -12 | +126 | + |
| S. B. | M | 41 | +38 | -11 | +150 | + |
| J. M. | F | 45 | +30 | +17 | - 16 | + |
| M. H. | F | 44 | +47 | -32 | + 73 | + |
| W. M. | F | 27 | +17 | - 4 | - 23 | + |
| I. M. | F | 23 | +88 | - 8 | + 35 | + |
| F. W. | F | 29 | +21 | -13 | + 43 | + |
| J. H. | F | 21 | +35 | -11 | + 70 | + |
| W. W. | F | 44 | +54 | + 8 | +105 | + |
| A. T. | M | 26 | +88 | - 8 | +106 | + |
| M. R. | F | 46 | +41 | - 9 | + 87 | + |
| A. B. | F | 32 | +27 | + 2 | + 66 | + |
| R. F. | M | 69 | +25 | -12 | + 65 | + |
| M. B. | F | 42 | +19 | + 6 | +100 | + |
| W. M. | M | 52 | +28 | +15 | + 56 | + |

TABLE II

Non-toxic Goitre.

| Case. | Sex. | Age. | B.M.R. %. | $a-v$ index. | Insulin-glucose response. | Creatinuria. |
|-------|------|------|-----------|--------------|---------------------------|--------------|
| A. H. | F | 55 | + 5 | + 8 | + 24 | + |
| F. T. | F | 39 | 0 | - 7 | + 21 | + |
| F. H. | M | 44 | +10 | +10 | + 59 | + |
| A. T. | F | 31 | +14 | + 1 | +108 | + |
| E. K. | F | 35 | + 3 | 0 | - 15 | - |
| E. M. | F | 35 | + 3 | + 2 | + 39 | + |
| M. R. | F | 36 | + 9 | + 2 | +164 | + |
| E. C. | F | 34 | - 7 | + 6 | + 39 | + |
| L. R. | F | 44 | - 3 | +11 | + 52 | + |
| A. T. | F | 31 | - 4 | +62 | +115 | - |
| S. H. | F | 35 | -15 | +57 | - 22 | - |
| J. S. | M | 42 | -11 | +18 | + 22 | - |
| N. S. | M | 32 | -12 | +16 | - 39 | - |
| A. T. | F | 31 | +14 | + 1 | +108 | + |
| A. E. | F | 28 | - 4 | + 6 | + 46 | - |
| J. L. | M | 28 | - 1 | + 2 | +128 | + |
| R. D. | F | 22 | - 7 | + 5 | + 42 | - |
| B. N. | F | 52 | + 4 | + 4 | + 28 | + |

Results

The peripheral insulin response in toxic goitre. Insulin failed significantly to increase the $a-v$ difference in 14 out of 17 cases of toxic goitre, the $a-v$ index being $< +10$; in the remaining cases the effect was slight (Table I). The mean arterial and venous blood-sugars of this group before, and thirty

and sixty minutes after insulin injection, were as follows: arterial blood-sugar 0.092, 0.116, and 0.144 mg. per 100 c.c.; venous blood-sugar 0.092, 0.115, and 0.148 mg. per 100 c.c. From these results it would seem that the muscles of the thyrotoxic subject, unlike those of the normal, do not respond to insulin by withdrawing increased amounts of glucose from the blood. In other words, toxic goitre is characterized by a high degree of peripheral resistance to insulin.

The peripheral insulin response in non-toxic goitre. In the large majority of non-toxic goitres the response to insulin in the peripheral tissues was poor (Table II). Thus in 12 cases the *a-v* index was $< +10$, while in 16 the index was below the lowest value we have seen in a normal subject. The mean arterial and venous blood-sugars in these cases were as follows: arterial blood-sugar 0.097, 0.105, and 0.128 mg. per 100 c.c.; venous blood-sugar 0.093, 0.098, and 0.124 mg. per 100 c.c.

We find, therefore, that peripheral resistance to insulin is not confined to those goitres manifesting toxicity, and we may draw the general conclusion that such resistance is not due to that aspect of thyroid function which is concerned with the regulation of the metabolic rate.

The effect of sub-total thyroidectomy on insulin resistance. Having established the existence of peripheral insulin resistance in thyroid disease, it became of interest to determine to what extent the thyroid must be held responsible. We have therefore re-determined the insulin-glucose response in 12 thyrotoxic and four non-toxic cases after sub-total thyroidectomy. The test was performed ten to twenty-six days after operation, in which time the patients had recovered from any post-operative upset and were well enough to leave hospital.

In the thyrotoxic group all but two showed an improvement in the peripheral insulin response after operation (Table III). On the whole, the magnitude of the response after operation was less than that shown by normal subjects, since in seven cases only was the *a-v* index $+25$ or more, but in all it was larger than before operation. Similarly, in the non-thyrotoxic cases there was improvement in the peripheral response, but in one this was still below normal (Table IV). It is evident, therefore, that in the majority of cases of goitre, quite independently of thyrotoxicosis, a marked improvement in the sensitivity of the peripheral tissues to insulin results from the removal of a large part of the thyroid tissue. In regard to those cases which failed to show this improvement after operation, two possibilities must be considered: (1) normal sensitivity might not be immediately restored by operation, and (2) although a large portion of the thyroid had been removed, the remaining tissue might still be exerting its morbid influence on the peripheral tissues. Whether these are the true explanations of the persistence of peripheral resistance after operation, and if so, their relative importance in any given case, are questions that can be answered only when we have had an opportunity to re-examine such cases after the lapse of a longer period.

In this connexion it is interesting that one of the toxic cases (D. W.), which after operation showed no improvement in the peripheral response to insulin, was re-admitted to hospital eleven months after discharge complaining of persistence of symptoms; these were tachycardia, dyspnoea, tiredness and excessive perspiration. On the second examination the blood-pressure

TABLE III

Toxic Goitre. Results Before and After Thyroidectomy.

| Case. | Before operation. | | | | After operation. | | | |
|-------|-------------------|---------------|----------------------------------|-------------------|------------------|---------------|----------------------------------|-------------------|
| | B.M.R. %. | a-v index. | Insulin- glucose response. | Creatin- uria. | B.M.R. %. | a-v index. | Insulin- glucose response. | Creatin- uria. |
| G. H. | +50 | +8 | +32 | + | -30 | +25 | +68 | — |
| D. W. | +39 | +11 | +165 | — | -3 | +1 | -9 | — |
| S. B. | +38 | -11 | +150 | + | -43 | +41 | +130 | — |
| J. M. | +30 | +17 | -16 | + | -16 | +23 | +31 | — |
| M. H. | +47 | -32 | +73 | + | -19 | +25 | +4 | — |
| F. W. | +21 | -13 | +43 | + | -9 | +25 | +58 | — |
| W. W. | +54 | +8 | +105 | + | -28 | +52 | +18 | — |
| A. T. | +88 | -8 | +106 | + | -1 | +10 | +32 | — |
| M. R. | +46 | -9 | +87 | + | -3 | +4 | +34 | — |
| M. B. | +19 | +6 | +100 | — | +6 | +49 | +87 | — |
| W. M. | +28 | +15 | +56 | + | +4 | +74 | +2 | — |

TABLE IV

Non-Toxic Goitre. Results Before and After Thyroidectomy.

| Case. | Before operation. | | | | After operation. | | | |
|-------|-------------------|---------------|----------------------------------|-------------------|------------------|---------------|----------------------------------|-------------------|
| | B.M.R. %. | a-v index. | Insulin- glucose response. | Creatin- uria. | B.M.R. %. | a-v index. | Insulin- glucose response. | Creatin- uria. |
| A. H. | +5 | +8 | +24 | + | -13 | +40 | -26 | — |
| F. T. | 0 | -7 | +21 | + | -20 | +25 | +26 | — |
| E. K. | +3 | 0 | -15 | — | -13 | +41 | +54 | — |
| E. M. | +3 | +2 | +39 | + | -6 | +14 | +4 | — |

was 180/135, the B.M.R. - 8 per cent., and the a-v index +22. A small mass of thyroid tissue could be felt. It will be observed that there had been very little improvement in the peripheral response to insulin which before discharge from hospital was represented by an a-v index of +1. Further operation was not advised in this case.

The action of Lugol's solution on the peripheral insulin response. While we have not been able to make an extensive study of the effect of iodine on the peripheral response to insulin in thyroid disease, our observations suggest that this is probably erratic. Thus in one case the B.M.R. was initially +21 per cent. and the a-v index +13. After nine days treatment with Lugol's solution the B.M.R. fell to +1 per cent. and the a-v index was +54, showing a considerable increase in peripheral sensitivity. On the other hand, we have seen another clinically similar case in which, although the B.M.R. was reduced from +28 per cent. to +4 per cent. by Lugol's solution,

the peripheral insulin response was actually diminished, the *a-v* index changing from +15 to +5. It is our impression that in comparison with the B.M.R. the peripheral insulin resistance is less susceptible to iodine.

The central insulin response. As was explained at the beginning of this paper the action of insulin is exerted both in the peripheral tissues and in the liver, either or both of which may be the site of resistance. In diabetes an abnormal rise in the arterial blood-sugar in the insulin-glucose test is due to hepatic or central resistance to insulin and is quite independent of sensitivity of the peripheral tissues (Griffiths, 1938). Similarly in goitre we have observed that the marked peripheral resistance is not necessarily accompanied by central resistance, as is proved by the numerous instances in our results in which an *a-v* index of $< +25$ is associated with an insulin-glucose response of $< +70$. It is remarkable that in so many instances the arterial blood-sugar should be independent of the amount of sugar taken up by the peripheral tissues, and it is difficult to explain why this should be so. It is as though the mechanism in the liver were a kind of ball-valve, maintaining with the help of insulin a roughly constant sugar level in the arterial blood, whatever the loss to the peripheral tissues may be. In some cases of thyroid disease there is, however, an abnormal rise in the arterial blood-sugar, denoting central resistance to insulin. Those cases, eight toxic and five non-toxic, in which the insulin-glucose response was $> +70$ are examples of this form of resistance.

No correlation exists between central resistance and the type of goitre; this is also true for the age, B.M.R., *a-v* index and the duration of the disease. Central resistance may be diminished by iodine, and in most cases is abolished by thyroidectomy; there are, however, outstanding exceptions in which it persists after operation. Cases of the latter type are in the minority and are confined to the thyrotoxic group. It seems possible that the persistence of central resistance in these cases is only temporary; that given time it would disappear just as does the peripheral defect. It is interesting that post-operative central resistance is not associated with any abnormality in the peripheral response to insulin, a fact which confirms the independent nature of the two phenomena. In one only of the 35 untreated cases studied by us was central resistance associated with peripheral sensitivity.

Creatinuria in Thyroid Disease

Brief reference must be made to the occurrence of creatinuria in thyroid disease, since this is of interest in view of the suggestion that the creatine tolerance is of value as an aid in the diagnosis of thyroid disorders (Shorr, Richardson, and Wolff, 1933; Thorn, 1936), and its association with other diseases showing insulin resistance. Creatinuria is a normal event in childhood and disappears at puberty. Adult males do not, therefore, excrete creatine in the urine, but some females may do so from time to time, quite erratically. During pregnancy, and especially after delivery, large amounts

are excreted. It is well known that creatinuria is a feature of thyroid disease, particularly of thyrotoxicosis, and that it can be produced in animals by thyroid feeding, or by injection of the thyrotropic hormone of the anterior pituitary (Pugsley, Anderson, and Collip, 1934).

We have made some observations on the creatine output in goitre which, although few in number, are nevertheless of interest. In the main we have confined our examinations to a single twenty-four-hour collection of urine from patients taking an ordinary ward diet. Creatine was estimated by Folin's open-flask method. Of 17 toxic patients examined all showed a significant creatinuria; this was also the case in nine out of 18 non-toxic cases. The creatinuria was often marked, amounting to more than 200 mg. per diem. In general, the higher the B.M.R., the larger was the daily output of creatine, but there were striking exceptions, as Kepler and Boothby (1931) found. We have verified the observation of Palmer, Carson, and Sloan (1929) that Lugol's solution either diminishes or abolishes the creatinuria in thyroid disease, often with dramatic suddenness.

Although peripheral insensitivity to insulin is not invariably accompanied by creatinuria, from which it would seem that there is no relationship existing between them, it must be remembered that absence of spontaneous creatinuria on an ordinary diet cannot be regarded as proof of normal creatine metabolism, which can be established only by estimation of the creatine tolerance, a procedure we have not applied to our cases. It is interesting that apart from thyroid disease creatinuria occurs in such apparently dissimilar diseases as diabetes, acromegaly, dermatomyositis, arthritis, and the myopathies. Iodine, which diminishes the creatinuria of thyroid disease, is quite ineffective in these other forms of creatinuria.

In regard to creatinine it has been stated that the daily output of this substance, which according to Folin is approximately proportional to the body-weight, is not increased in thyroid disease (Palmer, Carson, and Sloan, 1929), by thyroid feeding (Schrire, 1937) or by injection of the thyrotropic hormone (Pugsley, Anderson, and Collip, 1934). In our experience, while it is true that the majority of cases of thyroid disease do not show excessive creatininuria, there are exceptions. Thus in two cases of toxic goitre, both young males, studied over a period of several weeks, there was constantly an excessive output of creatinine, sometimes amounting to as much as 100 mg. per diem in excess of the upper normal limit. The output became normal in two to three days after thyroidectomy. Creatininuria is increased in acromegaly, and it is interesting to recall that this disease is sometimes associated with hyperthyroidism, but the cases of goitre cited above were entirely free from acromegalic traits.

Discussion

The peripheral insulin response in thyroid disease. It is well known that the carbohydrate tolerance may be lowered by thyrotoxicosis. While the

fasting blood-sugar is normal, or even subnormal, ingestion of glucose results in some cases in a high and prolonged rise in the blood-sugar, and glycosuria (Denis, Aub, and Minot, 1917). That this loss of carbohydrate tolerance is associated with a diminished capacity to store glycogen is borne out by the observations that when thyroid is fed to an animal the liver loses nearly all its glycogen, and that this cannot be prevented by administration of carbohydrate (Coggeshall and Greene, 1933; Cramer and Krause, 1912; Johnston, 1934). Not only the liver glycogen, but also that of the muscles—though this is more resistant—is in time depleted. There is evidence that these effects are associated with some interference with the re-synthesis of glycogen from lactic acid.

From the results presented in this paper it is clear that the very considerable increase in the *a-v* difference which normally occurs when insulin is injected, or when it is secreted by the pancreas, usually fails to manifest itself in cases of goitre. We have assumed that this absence of an increase in the *a-v* difference is an expression of resistance to insulin in the peripheral tissues, but in view of the increased circulation rate which is a feature of some forms of thyroid disease, it might be argued that the resistance is more apparent than real; that actually the blood is passing through the muscles at an enhanced rate and that for this reason the amount of sugar removed per unit volume of blood is diminished, although the absolute amount withdrawn may be unaltered. There are two considerations which render this explanation of the diminished *a-v* difference unlikely: firstly, it would require an increase in the circulation rate many times greater than that observed even in severe thyrotoxicosis to diminish the *a-v* difference sufficiently to render it negligible; and secondly, the lack of any dependence of the peripheral disturbance on an increase in the B.M.R. In regard to the latter point there is good evidence that the circulation rate is not increased unless the B.M.R. is more than 15 per cent. above the normal (Goldberg, 1938). While we have not made a direct comparison of the circulation time with the behaviour of the *a-v* difference during the action of insulin, we believe that it is fair to state that although in some cases where the B.M.R. is particularly high the increased rate of blood-flow may be a contributory factor in diminishing the *a-v* difference, it is improbable that it assumes any significance when the B.M.R. is normal.

If it is accepted that the diminished *a-v* difference in thyroid disease is not due to an increase in the circulation rate, then we are forced to conclude that in the large majority of cases with thyroid disease, sugar is not taken up by the muscles at an increased rate in the presence of insulin, and further, since under normal conditions much of the sugar so retained is ultimately converted to glycogen, we must suppose that the formation of muscle glycogen is impaired. It is curious, however, that whereas this break-down in the peripheral utilization of sugar is very general in thyroid disease, it is by no means invariably accompanied by a disturbance of like nature and similar severity in the liver; it is true that in about one-third of the cases we

have investigated there was some weakness of the sugar-storing capacity of the liver, as evidenced by an increased insulin-glucose response in the arterial blood-sugar, but the remainder, despite a very poor peripheral response, gave no evidence of this. In thyroid disease the muscles are therefore apparently more susceptible to the anti-glycogenic influence than is the liver, a situation which is the reverse of that existing in the animal fed with thyroid substance.

At first sight it seems reasonable to suppose that the anti-glycogenic character of the peripheral tissues is conferred upon them by the thyroid hormone, but on further consideration it will be seen to be doubtful whether the peripheral resistance to insulin is, in fact, due to the unaided action of the thyroid. Firstly, the phenomenon is not conditioned by the B.M.R., occurring when this is high, but, on the other hand, frequently also when it is well within normal limits; and secondly, similar peripheral insulin resistance occurs in diseases, such as diabetes, acromegaly (without hyperthyroidism) and dermatomyositis, which are not usually regarded as being associated with thyroid disturbance; it may also be induced in the normal subject by a ketogenic diet, an effect which again can hardly be ascribed to the thyroid. Furthermore, Lawrence and McCance (1931) failed to obtain any evidence that the thyroid interferes either with the formation or storage of glycogen in the muscles of the rat. It would seem, therefore, that although the results of thyroidectomy indicate that the thyroid plays a role in the production of peripheral resistance to insulin in goitre, considerations such as we have enumerated suggest that it does so through the mediation of some extra-thyroid agency.

It is, indeed, difficult to imagine how the thyroid hormone could be in the circulation and affect the response of the body to insulin and yet not affect the metabolic rate. We can only infer either that a product of the thyroid other than thyroxin is responsible, which is most unlikely, or that there is some extra-thyroid factor at work, conditioned in some way by the abnormal thyroid gland. It is now generally believed that the changes in the thyroid in disease do not arise *de novo*, but that there are extraneous influences at work to which many of the symptoms are due. The idea that there was a nervous factor in the development of Graves' disease was in vogue many years ago and it has recently been revived in Labbé's (1933) conception of the disease as a combination of hyperthyroidism with a neuro-vegetative syndrome. This syndrome, which includes exophthalmos, goitre, tremor and tachycardia, is now believed to be related to the anterior pituitary. There are still many points in thyroid disease which are quite incapable of being explained, and until more is known there appears to be no alternative but to include insulin resistance among those symptoms which are independent of the changes in basal metabolism, but which are nevertheless frequently alleviated by thyroidectomy.

Central insulin resistance. There are reasons for supposing that in some conditions such as diabetes and starvation the liver does not respond normally to insulin, with the result that the arterial blood-sugar rises to an

excessive degree during the absorption of sugar; this is referred to as central, or hepatic, resistance to insulin. An interesting aspect of insulin action in the subject with disordered thyroid function is the not infrequent occurrence of this central resistance. We have discussed elsewhere (de Wesselow and Griffiths, 1938), in dealing with the problem of insulin resistance in diabetes, the possible causes of this type of resistance, and we have said that it might be due to depletion of liver glycogen, or to some alteration in the metabolic state of the liver cell, interfering with its capacity for glycogen storage, or again, that some extraneous influence, such as the pituitary, may possibly be involved. We cited in support of the first suggestion Graves' disease, as being a condition in which depletion of the liver glycogen is to be expected and in which we detected the occurrence of central resistance. At that time we were unaware that resistance of this kind might also be manifested in non-toxic goitre, and it now seems that in view of the fact that well-marked central resistance may be met with in cases having a normal B.M.R., it is unlikely, at least in such cases, that glycogen depletion is a factor to be reckoned with unless, indeed, such depletion is brought about by causes other than thyroxin to which reference has been made in connexion with peripheral resistance.

The muscles in thyroid disease. Thyroid disease is commonly associated with muscular changes, varying in degree from mild myasthenia to marked atrophy, which may be the first indication of its presence. Weakness of the quadriceps muscle has, in fact, been advanced by Boothby and Plummer (1937) and Lahey (1926) as a test for thyrotoxicosis. Some idea of the severity of the disability suffered by the muscles in this disease may be gained by the statement of Ayer, Means, and Lerman (1934), which is borne out by the experience of others, that in some cases it would seem that there are two distinct diseases, one affecting the thyroid, the other the muscles. Weakness, tiredness, and abnormally rapid onset of fatigue are complaints which are voiced by the majority of victims of thyroid disorder independently of whether or not the B.M.R. is raised; indeed these symptoms are frequently more pronounced in the absence of thyrotoxicosis, by which they tend to be overshadowed.

The frequency of the occurrence and the severity of myasthenia in thyroid disease lend to the disturbances in the muscular metabolism of carbohydrate which we have described an importance which can hardly be over-emphasized. There can be little doubt that these two aspects of the disease are related; in fact, it is our impression from the cases we have studied that the more severe the myasthenia the more likelihood there is that peripheral insulin resistance will be marked. It would, indeed, be surprising if such profound disturbances in the metabolic processes of the muscles did not lead, in time, to structural changes in the muscles themselves. So we find that diffuse degenerative atrophy of the cells, loss of striation, fatty infiltration, vacuolization and degeneration of the nuclei in all striated muscles have been described in exophthalmic goitre by Askanazy (1898). All muscle

groups were not found to be equally affected, nor were the same muscles necessarily involved in different patients. Dudgeon and Urquhart (1926) examined the ocular, cardiac, and skeletal muscles, in exophthalmic goitre and observed the presence of lymphorrhages of variable size; in every case the eye muscles were more severely affected than the skeletal muscles, while the changes in the cardiac muscle were least apparent. That the heart is little affected is interesting because the glycogen of the heart is extremely refractory to the action of thyroid. In addition to lymphorrhages Dudgeon and Urquhart described proliferation of the interstitial cells and sometimes a chronic interstitial myositis, associated with varying degree of atrophy of the muscle fibres. They noted the similarity between their findings in exophthalmic goitre and those of others (Buzzard, 1905; Mandlebaum and Celler, 1908) in myasthenia gravis, a point which is of particular interest in view of the occasional association of these two diseases in the same person (Allen, 1934; Cohen and King, 1932).²

We may summarize this important aspect of our work as follows: insulin, as we have shown, fails to promote the assimilation of sugar by the muscles in thyroid disease, from which we infer that glycogen is not formed at a normal rate in the muscles. Associated with this abnormality in the peripheral action of insulin there is frequently a disturbance in creatine metabolism as evidenced by creatinuria and a lowered tolerance to ingested creatine. Although proof is lacking, it is natural to associate these two defects, poor glycogen formation on the one hand, and defective creatine metabolism on the other, in view of the role of creatine in carbohydrate metabolism of muscle. Further, there is sound evidence that in addition to these metabolic changes, and probably because of them, actual structural changes occur in the muscles. When we add that peripheral insulin resistance, creatinuria, and myasthenia are found associated together in other diseases such as diabetes, acromegaly, dermatomyositis, &c., it will be apparent that they form a syndrome the study of which might enable us to bring these diseases into closer relationship with one another.

Peripheral insulin resistance and diagnosis. The main objects of our investigations were firstly to observe the incidence of diminished peripheral insulin sensitivity in thyroid disorders, and secondly to determine whether this peripheral abnormality afforded a means of detecting an aberration in the function of the thyroid in those cases in which the B.M.R., being unaffected, is not of any value. In this paper we have found it convenient to divide our material into two groups, toxic and non-toxic, on the basis of the B.M.R. This is virtually what is done in clinical practice, but the more we understand thyroid disease the more it will become apparent that this method of differentiation is beset by grave disadvantages. Already we find Morris (1931 a, b) expressing the view that too much emphasis has been placed on the

² In a personal communication the late Professor L. S. Dudgeon expressed the opinion that sections of muscle removed at biopsy from a case of dermatomyositis showed changes which closely resembled those seen in exophthalmic goitre.

B.M.R. in the interpretation of clinical data, and Rosenblum and Levine (1933) stating that a normal metabolism may not exclude active hyperthyroidism. It is true that the toxic cases, taken as a whole, exhibit the more pronounced symptoms which never leave any doubt in the mind concerning the advisability of drastic measures in treatment, but there is a growing body of evidence to show that the non-toxic goitres are frequently responsible for very distressing subjective symptoms, both physical and psychological (Mandlebaum and Celler, 1908; Wishart, 1929; Morris, 1931 *a, b*; Rosenblum and Levine, 1933; Rasmussen, 1937; McEwan, 1938). Prominent among these are cardiac irregularities (auricular fibrillation and flutter) and myasthenia. In severity and duration thyrotoxicosis, as is well known, may show marked variability in different patients; thus in some it is rapidly progressive, while in others there may be periods of remission alternating with exacerbations of the disease which may show increasing severity. Unless frank thyrotoxicosis is present, detection of the underlying thyroid state may be difficult if not impossible.

The view that toxic goitre is not a simple disease, but a combination of hyperthyroidism with a neuro-muscular syndrome, was advanced by Labbé (1933). In a recent communication Rasmussen (1937) similarly separates the thyroid syndrome into three parts: (*a*) thyrotoxicosis, (*b*) psychoneurosis, and (*c*) exophthalmos. He stresses the possibility of a dissociation of these different aspects of the disease both before and after thyroidectomy or non-operative treatment. The advantage of this way of looking at thyroid disease becomes obvious if we imagine the rise in the metabolic rate and persistent tachycardia, in other words the thyrotoxicosis, to be banished from toxic goitre; we are then left with a symptom complex which, while of great clinical importance, can be baffling in diagnosis because of the obscurity of the thyroid background.

Rasmussen refers to this symptom complex as *non-thyrotoxic Graves' disease*, or the *psychoneurotic syndrome*. This syndrome may be suspected from the following signs: lassitude and asthenia, often in marked degree, palpitation of the heart, either continuous or intermittent, labile pulse-rate and vasomotor system, mental instability, irritability, tremors, insomnia, &c., According to Rasmussen this psychoneurotic syndrome must be regarded as constituting one part of the Graves' disease, thyrotoxicosis and eye signs the other; in some patients the former predominates, in others the latter. Thus it is possible for quite marked thyrotoxicosis to be associated with only slight evidence of the psychoneurotic syndrome, but this is perhaps less common than the opposite state in which the psychoneurotic syndrome dominates the picture, and in which there is little or no thyrotoxicosis. Rasmussen observed that in a number of cases of Graves' disease the psychoneurotic syndrome was still in evidence many months after surgical or radiological treatment, often in so marked a form as to interfere with the patients' working capacity, although there was no sign, from the pulse-rate and the B.M.R., of thyrotoxicosis.

This non-toxic type of Graves' disease is not exhibited only by cases of exophthalmic goitre after operation, but is frequently to be met with in patients who, particularly when at rest in bed, exhibit none of the signs of thyrotoxicosis. Many of these cases, when first seen by their doctors or in the out-patient clinic, present symptoms pointing to Graves' disease. They complain of increased fatigability, which may be marked and unaccompanied by other definite symptoms; of attacks of palpitation often lasting for more than an hour; of sweating, nervousness, dyspnoea; the pulse is frequently rapid, and there may be a coarse tremor unmistakably different from the fine vibratory form of true thyrotoxicosis. Ocular changes are commonly absent, and there may not be a palpable goitre. These symptoms vary considerably in individual cases, and it is uncommon to find all of them equally marked; on the one hand they may be suggestive of severe thyrotoxic Graves' disease, on the other the Graves' symptoms may be lacking, and weakness and paroxysmal attacks of tachycardia are the chief complaints. If these patients are admitted to hospital the symptoms become less pronounced, sometimes with amazing rapidity; the pulse-rate falls to a normal level, and the B.M.R., if determined after the lapse of a day or so, is usually found to be within the normal limits. In general, these patients belong to the borderline thyroid states which have been described as 'fruste' or larval hyperthyroidism, 'Basedowoid', neurocirculatory asthenia, autonomic imbalance, &c. The difficulty of arriving at a diagnosis in these cases is undoubtedly increased by the existence of so-called anxiety states which simulate thyroid disease in the closest possible manner. The thyroid element, if present, may reveal itself during prolonged observation, but more often than not it fails to do so until some cardiac, intestinal, neurological, or other feature, after causing much chronic disability, assumes a severity which makes a careful investigation imperative.

It is frequently a difficult matter, when one is confronted with cases of this type, to decide whether the symptoms are due to disturbances in the function of the thyroid or to an anxiety state, a difficulty which we believe mainly to be due to the crudity of our present methods of evaluating thyroid function. It is in this connexion that resistance of the muscles to insulin, which, as we have shown in this paper, is a feature of disordered thyroid function even when the basal metabolism is unaffected, affords a possible method of facilitating diagnosis. If a patient presenting the symptoms of non-toxic goitre, when tested according to the method we have described, is found to be resistant to the peripheral action of insulin, as evidenced by a small *a-v* index, there are, as our results show, good grounds for concluding that in all probability the thyroid is functioning abnormally. Further evidence which may be helpful can often be obtained from an examination of the urine for creatine while the patient is taking a full diet, or possibly better still, by estimation of the creatine tolerance. Differentiation of goitre states from others, such as diabetes, acromegaly, dermatomyositis, &c., which may show similar metabolic defects, presents no difficulty. Enough

has been said to describe the abnormal behaviour of the tissues and the incidental nature of the B.M.R. in goitre; we hope that others will be induced to experiment with this remarkable aspect of the disease.

Summary

1. The responses of a group of patients with toxic and non-toxic goitre to the insulin-glucose test of insulin sensitivity were determined. With this test we were able to estimate (a) from the changes in the arterio-venous blood-sugar difference the sensitivity of the peripheral tissues (muscles) to insulin, and (b) from the behaviour of the arterial blood-sugar the central, or hepatic, sensitivity. In toxic goitre the peripheral insulin response is either poor or negligible, denoting an impairment of the power of the muscles to utilize carbohydrate; this is referred to as peripheral insulin resistance. A similar condition of resistance is found in many cases of non-toxic goitre in which, although the B.M.R. is not raised, other signs suggestive of thyroid disturbance, such as intermittent tachycardia, increased fatigability, nervousness, &c., are present.

2. In some cases of goitre, both toxic and non-toxic, central resistance to insulin is present. This state may be described as an enfeeblement of the normal action of insulin in promoting storage of sugar in the liver.

3. In both toxic and non-toxic goitres, with very few exceptions, peripheral insulin resistance is considerably diminished by sub-total thyroidectomy. Possible reasons for the failure of some cases to show improvement in sensitivity are advanced. Central resistance is also in general abolished by thyroidectomy, but again it is occasionally unaffected.

4. The possible relationship between peripheral insulin resistance and myasthenia, which is a prominent symptom of both toxic and non-toxic thyroid states, is stressed. In this connexion the creatinuria which is a common feature of these thyroid disorders is of particular interest, more especially in view of the association of peripheral insulin resistance, creatinuria, and myasthenia in other diseases such as diabetes, acromegaly, and dermatomyositis.

5. The clinical pathology of thyroid disease is discussed. Emphasis is laid on the importance of the non-thyrotoxic or psychoneurotic element in goitre, which is manifested by many vague but nevertheless subjectively real symptoms, on the incidental nature of the B.M.R., and on the difficulty of discovering the thyroid background which exists in many cases. In view of the frequency with which we have encountered peripheral insulin resistance in cases of this type it is suggested that estimation of this factor might prove to be a valuable method of detecting possible aberrations of thyroid function in patients who, while not thyrotoxic in the sense that they have a raised metabolism, nevertheless complain of weakness, increased fatigability and symptoms of a cardiac or nervous character.

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FURTHER STUDIES OF PLASMA LIPIDS IN TOXIC GOITRE: EVIDENCE SUGGESTING A BIMODAL DISTRIBUTION¹

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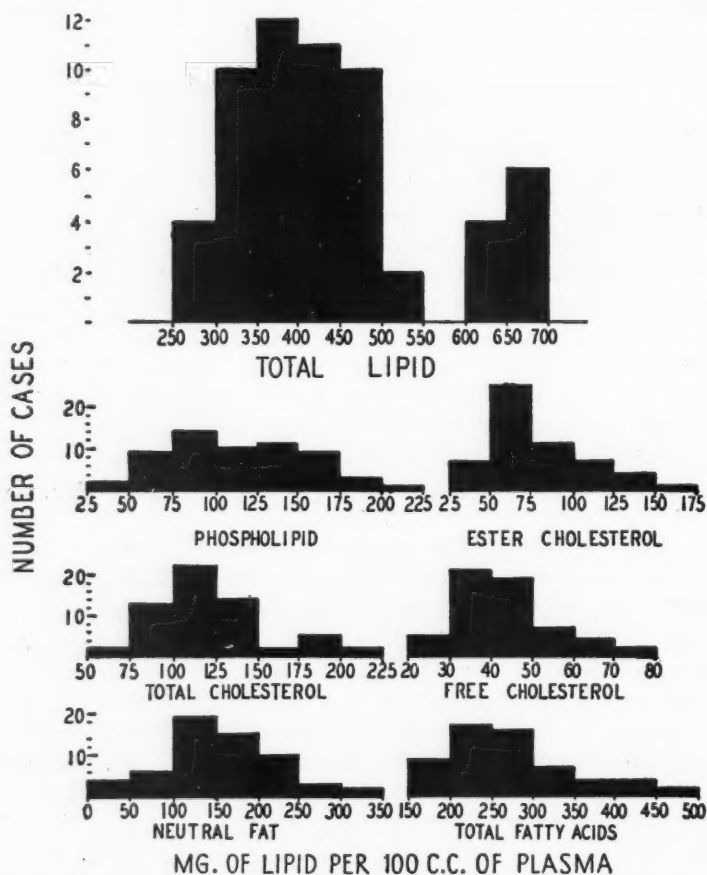
We have reported that the concentration of lipids in human blood-plasma is decreased in patients with toxic goitre (Boyd and Connell, 1937 *a*) and elevated following sub-total thyroidectomy (Boyd, 1936), increased in patients with myxoedema (Boyd and Connell, 1937 *b*), and decreased by thyroid feeding (Boyd and Connell, 1936). These findings indicate that there exists an inverse relationship between plasma-lipid content and what is generally considered the degree of thyroid activity. The results extend and confirm the many recent reports of a similar inverse relationship between thyroid function and the content of blood-cholesterol.

More specifically in connexion with the present communication, we have described toxic goitre in man as being characterized by the presence of a lipopenia in which the plasma content of most lipids is significantly subnormal, with no essential lipid changes in the red blood-cells (Boyd and Connell, 1937 *a*). Applying Chauvenet's (1888) criterion to the latter data, it may be calculated that the limiting classes beyond which extreme variants may be rejected as probably not belonging to the distribution are 268 and 588 mg. per cent. While preparing the manuscript of our (1937 *a*) paper, two analyses were performed on patients with hyperthyroidism in which total lipid values beyond 588 mg. per cent. were encountered. Since we did not have an opportunity of confirming these two high values, and since the previous homogeneous values had been tabulated, we did not include the two high values in our previous report (Boyd and Connell, 1937 *a*). Subsequent work has confirmed the wisdom of statisticians in stating that extreme variants eliminated by Chauvenet's criterion should not be suppressed in publishing the data. In the interval since submitting our original communication on toxic goitre we have met eight additional cases in which the plasma-lipid content was relatively high, in contrast to the usual finding of low values for plasma-lipids in hyperthyroidism. We have therefore found a total of 10 relatively high plasma-lipid values in a total of 59 cases of toxic goitre or hyperthyroidism studied, and this incidence of one in six appears to us too high to be neglected. A larger series of cases is obviously

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necessary to form the basis of a final decision on the validity of this apparent bimodal distribution, but as the collection of data will take several years, we wish to present a preliminary communication.

The heterogeneous nature of this clinically apparently homogeneous group of patients may be seen in the histograms, in which lipid analyses have been



Histograms of the frequency distribution of plasma-lipids in 59 patients with toxic goitre.

reported as histograms representing the frequency distribution of total lipid and of component lipids of blood-plasma in the 59 cases. All patients studied were from the Medical and Surgical Divisions of the Kingston General Hospital, and the analyses were performed by methods used in previous reports. The appearance of the histograms above would suggest the occurrence of a bimodal distribution of variants which appears reasonably definite for total lipid, and in view of this and of the shapes of the histograms, probably also for certain of the other lipids. There are two possible explanations of

this frequency distribution. Firstly, it may be the result of too few cases. We realize that, in spite of the statistical analysis to be deduced below, a larger series of cases is necessary eventually to prove or disprove a double frequency distribution. We hope to be able to offer such a series in due time. The second possible explanation of the data is that while patients diagnosed as having toxic goitre or thyrotoxicosis or hyperthyroidism may all appear similar clinically, there may in reality be two different conditions, one characterized by a lipopenia and the other by a high normal or slightly lipaemic plasma lipid content. Or it is possible that there may be two stages of the same disease characterized by different values for the concentration of lipids in blood-plasma.

Recognizing the desirability of additional data, nevertheless we may proceed to apply statistical criteria to the available figures. The problem is whether or not the results may be taken to indicate the probable presence of two frequency distributions within the group of cases reported. The histogram for total lipid presents the more striking appearance of a bimodal distribution, and for the purpose of the present communication values for total lipid may be selected for statistical analysis. It is possible first to prove by Chauvenet's (1888) method that the high total lipid values shown in the group to the right of the histograms probably do not belong to the main distribution. The mean value for total lipid of the entire group is 440 mg.

per cent. with a standard deviation of 59 mg. The argument, $k \frac{2n-1}{4n}$ has a value of 0.496, and the figure corresponding to this entry in Chauvenet's tables is 2.65. The limiting deviation is therefore 2.65×59 , or 156. The limiting classes of the distribution then become $440 - 156$ and $440 + 156$, or 284 and 596 mg. per cent. total lipid. All of the 10 high values for total lipid in the histograms are above the upper limiting class and hence probably do not belong to the distribution. In a similar manner, the limiting classes of total lipid values previously reported in hyperthyroidism (Boyd and Connell, 1937 *a*) may be shown to be 268 and 588 mg. per cent., which are similar to those found herein, and again would indicate the improbability of the high values of the histograms belonging to this distribution.

Having shown that the high total lipid values probably do not belong to the main distribution, we may proceed to consider the results as two groups and apply confirmatory criteria concerning the significance of the difference between them. The mean of the low total lipid group of 49 cases is 397 mg. per cent. with a standard deviation of 64 mg. and a standard error of 9.1. The mean of the 10 high total lipid values is 652 mg. per cent. with a standard deviation of 14 mg. and a standard error of 4.4. The standard deviation of the mean of the high total lipid group is remarkably low and will probably be found greater in subsequent work. However, though it were considerably higher and of the same order as the standard deviation of the mean total lipid of the lower group, the significance of the difference between means would not be materially affected. The mean difference of the total lipid of

the high and low groups is 255 mg. and the standard deviation of the mean difference is 10 mg. Since a mean difference which is twice its standard deviation indicates a reliable difference between the means, there is an abundantly significant difference between these high and low means, the mean difference being over 25 times its standard deviation. From the point of view of distribution, more than 95 per cent. of values in the low group may be expected to lie below more than 95 per cent. of values in the high group. This statement is based upon the fact that the lower mean total lipid plus twice its standard deviation gives a figure which is lower than the higher mean minus twice its standard deviation. This statement would still hold even if the standard deviation of the higher mean were eventually found to be about the same as that of the lower mean, which will probably be the case.

Although possibly superfluous in view of the above deductions, we have in addition employed two other criteria of significance applicable to small numbers of samples and in which the degree of freedom is taken into account accordingly. The first formula used is that of Tippet (1931)

$$t = \frac{M_1 - M_2}{s \sqrt{\left(\frac{1}{N_1} + \frac{1}{N_2}\right)}}$$

where

$$s = \sqrt{\left(\frac{N_1\sigma_1^2 + N_2\sigma_2^2}{(N_1 - 1) + (N_2 - 1)}\right)}.$$

Applied to the total lipid values of the high and low groups, the value of t may be shown to be 5.0, or almost twice the tabular value of 2.80, which is the minimal value given by Tippet as indicative of a significant difference with the given degrees of freedom. In this manner there has been shown again a significant difference between the two groups.

That the variabilities of the two total lipid groups are significantly different is further shown by the formula of Snedecor (1934) which is

$$F = \frac{\sigma_1^2}{\sigma_2^2}.$$

The calculated value for F of the present two variabilities is 20.9 which is four times as great as the tabular value of 4.51 given by Snedecor as the minimal value indicative of a significant difference.

By any and all of the various statistical criteria used, the present results indicate that there exist two distinctly different groups of total lipid values amongst the cases of toxic goitre studied. There remains only the possibility that further work will provide figures which will fill in the class frequencies between the two modes shown in the histograms, a possibility which is not likely to occur. Further figures would be desirable, however, before a statistical analysis is made of the distribution of the component lipids shown in the histograms. In general, but not always, an analysis giving a high total lipid also gave high values for the component lipids. A striking bimodal distribu-

tion was not seen with the available data until the cumulative effect of several relatively high component lipid values was summed in the total lipid.

In three of the 10 thyrotoxic patients with relatively high plasma-lipid values, repeated analyses were made both before and after sub-total thyroidectomy. Analyses, subsequent to the initial ones before operation and during iodination and rest, showed a tendency for the lipid values to increase still further. The total lipid values immediately before operation were in the three cases respectively 829, 787, and 751 mg. per cent. In one case no consistent change in lipid values occurred as late as 2 months after operation. One of the patients died in a 'thyroid storm' immediately after operation. We do not at present assume any relationship between this death and the high plasma-lipid content, because we have other instances of post-operative crises and death in patients showing the usual lipopenia before operation.

McGee (1935) reported blood-cholesterol values in 16 thyrotoxic patients and found the average well below the normal. Included in his series were two values which were abnormally high in thyrotoxic patients who responded satisfactorily to sub-total thyroidectomy. The attention given by Means (1937) to these exceptions in McGee's work shows that he attached unusual interest to them, although he does not comment further. The incidence of relatively high values for cholesterol in McGee's work was one in eight, which corresponds fairly well with the incidence found herein.

Summary

1. Lipid analyses by oxidative micro-methods of 59 cases of toxic goitre revealed a lipopenia in the blood-plasma of 49 patients, and high normal or slightly lipaemic values in the plasma of the remaining 10 patients.

2. A statistical analysis of the results indicates the probability of two significantly different groups within the total series. A larger series of cases must be studied in order to test the existence and the meaning of such a bimodal distribution.

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PLASMA LIPIDS IN ANXIETY STATES AND THEIR COMPARISON WITH THE LIPOPENIA OF HYPERTHYROIDISM¹

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THE differentiation between hyperthyroidism and anxiety states is a well recognized diagnostic difficulty. The so-called anxiety state (Henderson and Gillespie, 1930) is probably the condition which is most commonly diagnosed incorrectly as mild hyperthyroidism (Owen, 1937), but not infrequently a true mild hyperthyroidism may be classed as an anxiety state (Means, 1937). It is not the purpose of the present communication to discuss the differentiation of symptoms and signs common to the two conditions; this phase of the problem has been treated in a number of recent articles, for example by Owen (1937). Our report describes an investigation designed to determine if the estimation of plasma lipids could be used as a laboratory aid in the differential diagnosis.

Previous tests for this purpose have proved disappointing. Tests which have been used include the determination of the basal metabolic rate (Means, 1937), glucose tolerance (Owen, 1937), and blood-iodine (Curtis, 1936). The difficulty which has consistently appeared in all of such studies is that the results obtained in anxiety states tend to extend beyond the normal frequency distribution and so overlap any pathological distribution of results with which a comparison is being made. It is usually possible to demonstrate a significant difference between means, but because of the abnormally wide distribution the method is of little diagnostic value in any single case. A similar result was obtained in the present work. Metabolic studies which have been made to date show that metabolism in anxiety states is usually found to be normal, but that extreme variants are found extending into the realm of greater or less than normal. This suggests the probability that the anxiety state as we diagnose it to-day is not a single entity, but a mixture of conditions.

During the past four years plasma lipids have been estimated by oxidative micro-methods previously described (Boyd and Connell, 1937), on a total of 76 patients at the Kingston General Hospital in whom a diagnosis was made of anxiety state. The results are summarized in Table I and compared with values in normal adults determined by the same methods. It

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may be noted from Table I that plasma-lipid values both considerably below and considerably above the normal range were encountered in anxiety states, and the mean values were, in general, lower than normal. The standard deviation of the mean difference between the distribution of values in anxiety states and in normal adults indicates a statistically significant

TABLE I

Statistical Summary of Results Obtained in the Differential Lipid Analyses of Blood-plasma of 76 Patients with an Anxiety State.

The Results are expressed in mg. of Lipid per 100 c.c. of Plasma.

| Value. | Total lipid. | Composition of total lipid. | | | | | Phospho-lipid. |
|--|--------------|-----------------------------|--------------------|--------------|--------|-------|----------------|
| | | Neutral fat. | Total fatty acids. | Cholesterol. | | | |
| | | | | Total. | Ester. | Free. | |
| <i>Anxiety States.</i> | | | | | | | |
| Minimum | 290 | 2 | 156 | 94 | 46 | 23 | 73 |
| Maximum | 920 | 367 | 573 | 241 | 175 | 109 | 273 |
| Mean | 546 | 184 | 334 | 152 | 99 | 53 | 144 |
| Standard deviation | 118 | 74 | 84 | 34 | 28 | 15 | 45 |
| Standard error | 14 | 9 | 10 | 4 | 3 | 2 | 5 |
| Coefficient of variation | 22 | 40 | 25 | 22 | 28 | 28 | 31 |
| <i>Normal Adults.</i> | | | | | | | |
| Mean | 617 | 154 | 362 | 181 | 128 | 53 | 195 |
| Standard deviation | 75 | 77 | 62 | 22 | 23 | 10 | 37 |
| Standard error | 25 | 26 | 21 | 7 | 8 | 3 | 12 |
| Coefficient of variation | 12 | 50 | 17 | 12 | 18 | 19 | 18 |
| <i>Difference: Normal Adults minus Anxiety States.</i> | | | | | | | |
| Mean difference | -71 | +30 | -28 | -29 | -29 | 0 | -51 |
| Standard deviation of mean difference | 29 | 28 | 23 | 8 | 9 | 4 | 13 |

lowering of all the means, except those for neutral fat, total fatty acids, and free cholesterol. In view of the possibility of a heterogeneous distribution of samples in the anxiety state group, as noted above, we believe that caution should be exercised in concluding that the plasma-lipid values are significantly decreased in anxiety states. While there may be a significant difference between means, it is obvious from Table I that the distribution of values in anxiety states overlaps both the upper and lower limits of normal. This extensive variation is seen in Pearson's coefficient of variation which has been calculated and included in Table I. The average coefficient of variation was about one-third greater in anxiety states than in normal adults.

In general, then, the distribution of values for plasma lipids in anxiety states is about the same as normal, but tends to extend into both the lipaemic and lipopenic extremes. As a result of the latter tendency, there is more overlapping in the distribution of values between anxiety states and hyperthyroidism than between hyperthyroidism and normal. The lipid content of plasma in anxiety states has been compared with that previously found

in hyperthyroidism (Boyd and Connell, 1937), and the results summarized in Table II. All of the mean values in hyperthyroidism were below all of the mean values in anxiety states. In every instance the standard deviation of the mean difference was considerably less than one-half of the mean difference, so that statistically there was an abundantly significant difference

TABLE II

The Lipid Content of Blood-plasma in 76 Patients with an Anxiety State compared with that in 43 Patients with Hyperthyroidism (Boyd and Connell, 1937).

The Results are expressed in mg. of Lipid per 100 c.c. of Plasma.

| Value. | Total lipid. | Composition of total lipid. | | | | | Phospho- lipid. |
|---|--------------|-----------------------------|--------------------|--------------|--------|-------|--------------------|
| | | Neutral fat. | Total fatty acids. | Cholesterol. | | | |
| | | | | Total. | Ester. | Free. | |
| <i>Anxiety States.</i> | | | | | | | |
| Mean | 546 | 184 | 334 | 152 | 99 | 53 | 144 |
| Standard deviation | 118 | 74 | 84 | 34 | 28 | 15 | 45 |
| Standard error | 14 | 9 | 10 | 4 | 3 | 2 | 5 |
| Coefficient of variation | 22 | 40 | 25 | 22 | 28 | 28 | 31 |
| <i>Hyperthyroidism.</i> | | | | | | | |
| Mean | 428 | 126 | 258 | 122 | 81 | 41 | 125 |
| Standard deviation | 63 | 59 | 51 | 20 | 18 | 8 | 35 |
| Standard error | 10 | 9 | 8 | 3 | 3 | 1 | 5 |
| Coefficient of variation | 15 | 47 | 20 | 16 | 22 | 19 | 28 |
| <i>Difference : Anxiety States minus Hyperthyroidism.</i> | | | | | | | |
| Mean difference | -118 | -58 | -79 | -30 | -18 | -12 | -19 |
| Standard deviation of mean difference | 17 | 13 | 13 | 5 | 4 | 2 | 7 |
| Sum of two standard deviations | 181 | 133 | 135 | 54 | 46 | 23 | 80 |

between the means. This indicates that there is a reliable tendency for plasma-lipid values to be higher in anxiety states than in hyperthyroidism. However, the distribution of results considerably overlapped each other in the instance of every lipid. This is seen in the fact that the sum of the standard deviations considerably exceeded the difference of the means of each lipid.

In any given patient, having eliminated other lipotropic factors and reduced the diagnosis to either anxiety state or hyperthyroidism, the finding of a lipopenia would not necessarily rule out an anxiety state. Furthermore, and in view of the bimodal distribution described in the preceding paper (Boyd and Connell, 1939), the finding of high normal or slightly lipaemic values would not necessarily rule out hyperthyroidism. We therefore conclude that the estimation of plasma lipids is of limited value in the differential diagnosis between hyperthyroidism and anxiety states.

Summary.

1. A differential lipid analysis of blood-plasma was performed by oxidative micro-methods on 76 patients with an anxiety state.

2. The means of the concentration of plasma lipids in anxiety states were found significantly lower than normal and significantly higher than in hyperthyroidism. There was considerably more variation in results in patients with anxiety states than in either normal adults or in patients with hyperthyroidism. As a result the frequency distribution overlapped to the extent that the estimation of plasma lipids was found of limited value in the differential diagnosis of hyperthyroidism and anxiety states.

This work was aided financially by the Alice F. Richardson Fund of the Kingston General Hospital.

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OBESITY, HYPOGENITALISM, MENTAL RETARDATION,
POLYDACTYLY, AND RETINAL PIGMENTATION
THE LAURENCE-MOON-BIEDL SYNDROME¹

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IN a previous article on the Laurence-Moon-Biedl syndrome (Cockayne, Krestin, and Sorsby, 1935) an analysis was given of the 101 cases collected from the literature up to 1935. The many articles that have appeared since then have brought forward some new aspects of the affection, justifying a further analysis in the present report on two families.

1. *Review of Literature*

The most significant additions to knowledge bear on the mode of inheritance of the affection, the tentative demarcation from allied syndromes, and the post-mortem findings in three cases.

1. *Mode of inheritance.*

(a) *Racial incidence.* The cases previously collected were all of the Caucasian race. Three cases from Japan have now to be noted (Yamamoto, 1935; Hayashi, Uyeno); there is also one from Egypt (Zaky, 1936).

(b) *Antecedents.* As in the earlier cases, there are no reports of the direct inheritance of the syndrome, with the possible exception of van Bogaert's and Borremans's (1936) case. A healthy child born to an affected woman is reported by Biemond (1934), whilst Amyot (1937) notes three pregnancies ending in abortion in another patient. On the other hand, many reports give histories suggestive of the partial presence of the syndrome in ascendants and their relatives.

Obesity. This is noted in the mother by Pesme and Hirtz (1937), and by Giannini (1933); in the mother's family by Aschner (1927); in the father and frequently in his family by Copperstock (1937); and in a paternal uncle (obesity and blindness) by Lhermitte and Bollack (1936). Ricci (1934) observed in one family a paternal uncle showing obesity, mental deficiency, and night-blindness, and in another a maternal aunt with the same signs. Yamamoto (1935) reports obesity in the paternal grandmother, her sister, and their mother; a niece of the paternal grandmother was also obese; obesity in two sisters of the paternal grandmother was noted by Amyot (1937). Biemond (1934) recording an isolated case, the offspring of healthy parents, describes obesity in a paternal uncle, obesity with retinitis pigmentosa in a paternal aunt, the grandmother herself being obese.

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Mental defect. As already noted this was observed in association with obesity by Ricci (1934) in two families. In association with atypical retinitis pigmentosa it was observed by Mutch (1937) in two maternal uncles, the mother herself being normal. Insanity in a maternal cousin is reported by Klenerman (1935), whilst mental taints, as also retinitis pigmentosa, are noted extensively in the mother's family by van Bogaert and Borremans (1936). In Steinberg's (1937) cases the mother and maternal grandmother were probably mentally defective.

Retinal degeneration. Apart from the retinal degeneration in association with obesity (Ricci, 1934, two families; Lhermitte and Bollack, 1936; Biemond, 1934), and with mental deficiency (Mutch, 1937; van Bogaert and Borremans, 1936) already noted, Biemond reports retinitis pigmentosa in a maternal cousin and Becker (1937) 'chorio-retinitis' in the mother. Van Lint and van Bogaert (1934) note blindness and syndactyly in an uncle, whilst Amyot (1937) records night-blindness in the paternal grandmother. Nystagmus in the mother was present in Aschner's (1927) and Kornfeld's (1933) cases.

Polydactyly. Two thumbs in a paternal great-uncle is noted by Lhermitte and Bollack (1936) and polydactyly in the great-grandfather by Frank (1936). Polydactyly in a paternal great-uncle is also noted by Molitch, Gladen, and Pigott (1935). Syndactyly with blindness was noted, as already observed, by van Lint and van Bogaert (1934) in an uncle. Amyot (1937) records joint anomalies in the fingers of a paternal uncle, his four daughters, and in two granddaughters, the offspring of one of these four. Syndactyly in a maternal grandfather is reported by Warkany, Frauenberger, and Mitchell (1937) whose patient and three of her cousins also showed this defect.

Other defects. Parkinsonism in the father is noted by Jenkins and Poncher (1935) and a deaf mute aunt is reported by Lhermitte and Bollack (1936). Congenital cerebello-pyramidal degeneration in a collateral branch is reported by van Lint and van Bogaert (1934).

(c) *Sibship.* As in the earlier series, suggestive lesions in deceased members of the family are a striking feature. Occasionally, the full syndrome seems to have been present, as in the cases reported by Savin (1935), Spektor and Sokolov (1937), Franceschetti and Streiff (1936), Molitch, Gladen, and Pigott (1935), and Copperstock (1937). Congenital heart disease in a brother who died at 8 years is noted by Arena (1937); obesity in a sister at 8 years by Pesme and Hirtz (1937 *b*); congenital defect of the spine in a sister who died shortly after birth by Jenkins and Poncher (1935), whilst Lhermitte and Bollack (1936) noted spina bifida in a half-brother, and epilepsy in another half-brother. Spektor and Sokolov (1937) also noted the syndrome in a maternal cousin.

(d) *Consanguinity.* Consanguinity in the parents is noted by Judge (1937), Spektor and Sokolov (1937), Franceschetti and Streiff (1936), Steinberg

(1937), Hayashi, and by Uyeno. That there was no consanguinity is reported by Mutch (1937), Savin (1935), Klenerman (1935), Gillespie (1937), Weissberg (1935), Groos (1935), Molitch, Gladen, and Piggott (1935), van Bogaert and Borremans (1936), Gabriélidès (1937), Villegas (1935), Ricci (1934) three families, Hutton (1932), Zaky (1936), and by Yamamoto (1935).

(e) *Wassermann reaction*. Except for two cases with positive reactions reported by Bietti (1937) this was negative in every case in which it was taken; and it was taken in most instances.

2. *The components of the syndrome.*

(a) *Mental defect*. This was absent in the cases reported by Marks (1936), Becker (1937), and Weissberg (1935); and in the three sibs described by Hutton (1932).

(b) *Adiposity*. This was a constant feature in all the patients described, except in one of the two brothers described by van Lint and van Bogaert (1934), one brother tending to be fat and the other thin. The boy in family M. reported in the present paper was distinctly obese as a child, whilst now at the age of 21 years he is distinctly lean, and has been so for the past five years.

(c) *Hypogenitalism*. The birth of a normal child to an affected woman described by Biemond (1934), and the occurrence of three pregnancies ending in spontaneous abortions in another patient described by Amyot (1937) has already been noted. The absence of hypogenitalism is recorded by Marks (1936), Roger and Farnarier (1937), Molitch, Gladen, and Piggott (1935) Case 1; Copperstock (1937) Case 1; Biemond (1934) Cases 1 and 2 in family X, and Spector and Sokolov (1937).

(d) *Polydactyly*. As in the earlier series the polydactyly was post-axial, and every variation of an accessory sixth finger or toe, ranging from small fibrous skin-clad nodules without a bony centre to a fully developed digit, has been recorded. Accessory digits on the two hands and feet were observed by Arena (1937), Savin (1935), Groos (1935), Roger and Farnarier (1937), Biemond (1934), and by Paton (1936) amongst others; on the two hands and one foot by Weissberg (1935); on the two feet only by Mutch (1937), and Lhermitte and Bollack (1936); on the two feet and one hand by Molitch, Gladen, and Piggott (1935), Steinberg (1937), and by others. In the family described by Hutton (1932), one member had an extra digit on each of the four extremities, a second on one hand and on one foot, and another on one foot only. In Steinberg's (1937) family one member had extra toes on both feet, a second on the two feet and one hand, and a third had no polydactyly at all. In the family described by Molitch, Gladen, and Piggott (1935), a child who died at 8 years from congenital heart disease was said to have had seven fingers on each hand and six toes on each foot. In a case of Bietti (1937) the two feet and the left hand showed hexadactyly; the right

hand had seven fingers, two being fused into one; there is no X-ray illustration of this condition.

Syndactyly in association with polydactyly is described by Arena (1937), Mutch (1937), Lhermitte and Bollack (1936), Klenerman (1935) whose patient showed bony fusion of the middle and ring fingers, Judge (1937), Gabriélidès (1937), and by Spektor and Sokolov (1937). Syndactyly without polydactyly is noted by Warkany, Frauenberger, and Mitchell (1937). Deformity of hands and feet—ill shapen rather than distorted by gross structural anomalies—are described as variants to polydactyly or as an association of it by Pesme and Hirtz (1937 *b*), Mutch (1937), Paton (1936), van Bogaert and Borremans (1936), and by van Lint and van Bogaert (1934), the patients of the last showing brachydactyly. An unusual variant is noted by Amyot (1937), whose patient (and possibly also some of her ascendants) showed stumpy hands with stunting of the small fingers in each hand from dystrophy of the second phalanx, whilst the feet showed absence of the second phalanges in all but the big toe.

(*e*) *Pigmentary degeneration of the retina (retinitis pigmentosa)*. In Zaky's (1936) case there was no definite fundus lesion at 14 years, but there is now thinning of the retina without pigmentary change. The third member, aged 10 years, of the family reported by Molitch, Gladen, and Pigott (1935) is also said to have had normal fundi. Marks (1936) notes atypical retinitis pigmentosa in a boy of 16 years, who at 10 had been regarded as having normal fundi by one ophthalmologist, whilst another thought he had a macular lesion. The second case of Copperstock (1937) is reported as having normal fundi at the age of 2 years. As in the previous series most observers speak of the presence of atypical, rather than of typical retinitis pigmentosa. The replacement of even atypical retinitis pigmentosa by a macular dystrophy of the type seen in cerebro-macular degeneration—as described in the second family of the previous study—is reported by Savin (1935), Mutch (1937), Roger and Farnarier (1937), and by Marks (1936).

(*f*) *Other defects*. These cover a considerable range. Dwarfing is noted by Mutch (1937), Lhermitte and Bollack (1936), Klenerman (1935), and by Molitch, Gladen, and Pigott (1935); cranial deformity by Lhermitte and Bollack (1936), Gillespie (1937), and Villegas (1935); hydrocephalus by Spektor and Sokolov (1937); oxycephaly by Rovinsky (1937); ptosis with facial asymmetry by Copperstock (1937) second case; facial palsy of the central type with other neurological symptoms by van Bogaert and Borremans (1936); kyphosis by Pesme and Hirtz (1937 *b*) and Klenerman (1935); lordosis by Becker (1937); genu valgum by Zaky (1936), Arena (1937), Pesme and Hirtz (1937 *b*), Groos (1935), and by Copperstock (1937); pes planus by Arena (1937), and Warkany, Frauenberger, and Mitchell (1937); atonic muscles by Becker (1937) as also by Pesme and Hirtz (1937 *b*) and by Lhermitte and Bollack (1936); cyanotic skin by the two last-named groups of authors. Deaf mutism is reported by Becker (1937), and was also seen in the three affected members of the family reported by Steinberg (1937);

congenital heart disease was the cause of death within thirty hours of birth of the case described by Villegas (1935). Adiposis dolorosa was possibly present in a case described by van Bogaert and Borremans (1936). Infantile glaucoma in one eye was possibly present in the second case of Pesme and Hirtz (1937 *b*).

(*g*) *Sella turcica*. This is generally reported as normal.

3. *Post-mortem findings*.

Three post-mortem records are now available. One by van Bogaert and Borremans (1936); a second—an incidental observation—by Loepp (1936), and the third a detailed examination by Griffiths (1938) of a case previously reported by him. The first refers to the elder of two affected brothers, whose mother was a member of a family tainted with mental disturbances and retinitis pigmentosa. This case was further complicated by the presence of symptoms suggestive of adiposis dolorosa, and also by right facial palsy of the central type and extensor spasticity of the lower limbs with exaggerated tendon reflexes. Radiography revealed an internal frontal exostosis, an anomaly also found in the brother. The post-mortem findings were essentially negative; macroscopically nothing abnormal was found, microscopically the centre of the stalk of the pituitary showed a band-shaped area devoid of nuclei, the surrounding tissue not showing any reaction—an appearance which, they state, was described by Kraus as seen in hypertension and as having no significance.

Loepp's (1936) patient died at 39 years from carcinoma of the oesophagus. He showed all the classical signs of the syndrome except polydactyly. Radiography showed his sella to be enlarged, and *post mortem* the stalk of the pituitary was found to support a minimal amount of pituitary tissue, the sella itself being filled with a cyst in whose wall epithelial rests were present.

Griffith's (1938) examination revealed a small uterus and adnexa, and abnormal kidneys with irregular deep lobulation and foetal histological structure. The thymus showed many fibrous bands breaking up the gland into islets of tissue; Hassall's corpuscles were small and very few in number. The pituitary body was small, and sections showed an excess of basophil cells. The frontal poles of the brain were shrunken, and a vertical section of the brain gave normal appearances. The histological abnormalities were slight, and consisted mainly of a paucity of cells in the tuberal nuclei.²

In none of these cases does the brain appear to have been studied for lipid products.

2. *Personal Observations*

In view of the large number of case reports now available, it will suffice

² Two further cases have since been studied. They are briefly mentioned by Riggs (1938) who considers the histological findings of the brain as indicative of abiotrophy. A fuller report is promised.

to report briefly the positive aspects shown by two new familial groups. Both these groups are Jewish and in both cases the parents are first cousins and are normal. The antecedents are clear.

The G. family. There were five pregnancies all going on to full term, the children all being boys. The eldest is alive and normal. The second died at 23 years from pneumonia; he was an inmate of Leavesden Mental Hospital and showed all the typical features of the Laurence-Biedl syndrome (mental deficiency, obesity, atypical retinitis pigmentosa, hypogenitalism, and polydactyly). The third and fourth boys died at 10 years and at 4½ years respectively; nothing definite could be established about them. The fifth is now 17 years old, is obese, mentally deficient, and is certified as a blind person. Extra digits on the ulnar sides of the hands were removed in infancy. There is fleshy syndactyly in both feet; the left foot shows fusion of the fourth and fifth digits, and in both feet there is fusion of the proximal parts of the second and third toes. Radiography shows no bony abnormality of hands or feet. The fundi show atypical retinitis pigmentosa with considerable pigmentary changes and optic atrophy. The testicles are undescended and the penis is small. There is marked flat foot.³

The M. family. There were eleven pregnancies, two ending in miscarriage. Of the nine children only one was a boy. The eldest child died at three weeks. The youngest daughter and the boy, her immediate senior in the family, are the only members affected.³

Samuel M., aged 21 years. At the age of 8 years he came under the care of Mr. R. C. Davenport, who remembers him as a very obese child. For the last four years he has become distinctly lean. Nine months ago he developed rheumatic fever which has left chronic endocarditis of the aortic and mitral valves. He is mentally defective to the degree of being unemployable. There is no distinct hypogenitalism and apart from scoliosis there are no skeletal abnormalities, but small fleshy excrescences on the ulnar aspects of both hands are present. There is violent nystagmus and the fundi reveal considerable retinal atrophy as shown by the dirty grey reflex and narrow arteries; pigmentary changes are absent, though the maculae suggest dystrophic disturbances.

Sarah M., aged 19 years, is stout, though not grossly obese. She, too, is so defective as to be unemployable; her fundi show the same changes as are seen in her brother; the right hand shows an extra finger on the ulnar side; menstruation is apparently normal.

3. Discussion

1. Allied conditions.

Nothing is to be gained by forcing a wide range of teratological anomalies into the clear-cut Laurence-Biedl Syndrome. It is possible that variants of the syndrome do occur, but the admission of these variants must await their observation in a family undoubtedly showing the syndrome in some other member—a course all the more necessary as allied and perhaps independent syndromes have been described.

³ These cases were shown at the Section of Ophthalmology of the Royal Society of Medicine in December 1936 (Avery and Sorsby, 1936).

(a) *Somatic and psychic infantilism, coloboma of iris, and skeletal anomalies.* Biemond (1934) reported the occurrence of this symptom-complex in a brother aged 19 and sister aged 31 years. Both showed pituitary infantilism, the brother in addition also showing coloboma of the iris in the right eye, and the sister a double thumb on the right hand, and kyphoscoliosis. In the case of the man the evidence for hypogenitalism was conclusive; in his sister menstruation had not occurred. Features suggestive of syringomyelia and ultimately leading to death, developed in the sister. *Post mortem*, a cerebral tumour (? glioma), hydrocephalus and hydromyelia were found, as also multiple polypi in the colon, some undergoing carcinomatous degeneration. The pituitary body was small. Van Bogaert and Delhay (1936) reported as a case of Biemond's syndrome a boy of 12 years who showed mental deficiency, adiposity, hypogenitalism, bilateral atypical coloboma of iris, kyphosis, and metabolic disturbances (lowered basal metabolism associated with eosinophilia, anomalies in water excretion, low lipid and cholesterol blood content). The boy was tall for his age, had a large head, and brachydactyly; the sella was normal. His two brothers both showed kyphosis; a maternal cousin showed pituitary obesity, mental deficiency, and kyphosis; one maternal aunt was obese, another showed obesity, mental deficiency, and kyphosis, and a third was an epileptic. Except for the absence of retinal degeneration and the presence of coloboma of iris, this particular case has more in common with the Laurence-Biedl syndrome than with the group described by Biemond (1934). An older observation by Ratner (1927), case 3 in his paper, which has passed down in the literature as a case of the Laurence-Biedl syndrome may be recalled in this connexion. Ratner's patient was obese, epileptic [mentally defective], and showed coloboma of the iris and choroid.

(b) *Mental deficiency, hypogenitalism, Friedreich's ataxia, and choroidal sclerosis.* In a family group described by Kapuscinski in 1934 two sisters, aged 30 and 14 years, and one brother aged 17 years, with ataxia of the type seen in Friedreich's disease, were mentally dull, and showed different stages of peripapillary choroidal sclerosis, most marked in the eldest, in whom it had led to blindness. All three were highly myopic. The eldest patient showed hypogenitalism (no menstruation); in the boy there was cryptorchism. The parents were not consanguineous and their family antecedents were clear. There were thirteen children, of whom only four survived, and one of these four was normal. Of the deceased members of the family, one had been seen by Kapuscinski when she was 24 and had papilloedema; she died three months later from pulmonary tuberculosis.

This group thus differs from the Laurence-Biedl syndrome in the absence of adiposity and polydactyly, and in the presence of ataxic signs. In this connexion it is worth recalling that the original cases of Laurence and Moon showed no polydactyly, that they had different degrees of 'a slouching heavy gait as if they were tipsy', and that furthermore Hutchinson who studied these patients ten years later, described the fundus appearances as

due to 'disease of the choroids' and stressed the presence of paraplegic symptoms.

(c) *Cerebellar ataxia, nystagmus, exophthalmos, and brachydactyly.* Biemond (1934) described the occurrence of these defects in a patient, who on the maternal side had a family history of severe manic-depressive psychosis, and on the paternal side, ocular anomalies (exophthalmos and possibly nystagmus). On neither side was there ataxia. One brother showed nystagmus, doubling of the thumb on the right hand, and cerebellar ataxia; another, brachydactyly and doubling of the upper lip; a third brother had ptosis; whilst a sister showed the same type of brachydactyly as the patient and the second brother, and also shortening of the fourth finger in each hand from a short, but normally formed metacarpal. Biemond holds that the syndrome represents fortuitous coupling of characters in this particular generation and is not inherited as a whole, for the subsequent generation is completely free from the syndrome, and almost entirely free from partial components.

This group is of interest in the association of skeletal defects with ataxia, an association not seen in the ataxic group described by Kapuscinski (1934).

(d) *Anomaly of stature and retinal degeneration.* Best (1902) briefly noted the occurrence of gigantism with 'congenital chorio-retinitis' and possibly also adiposogenital dystrophy in a boy of 8 years. More recently Böck and Risak (1934) described gigantism (height 183 cm.) in a man of 28 years suffering from retinitis pigmentosa, osteoma of the parietal bone, and spastic pes cavus; the patient was mentally dull and his bodily build suggested late eunuchoidism. The family history was clear and there was no consanguinity.

A more clearly cut picture is reported by Cockayne (1936) in a girl aged 8 and her brother aged 6 years, the two youngest and only affected children of a family of six, the offspring of healthy non-consanguineous parents. Both children were dwarfs, with small heads, slender bodies, unduly long legs, and the third and fourth fingers of the hands were directed mesialwards. Both patients showed retinal dystrophy of the 'pepper and salt' pattern, most noticeable in the central areas, and both were deaf.

(e) *Obesity with microphthalmos and other ocular anomalies.* Cavallacci (1937) reports obesity of the pituitary-diencephalic type in a mother and daughter, both of whom had microphthalmos unequal in the two eyes, and both also showed calcareous cataract in one eye. A son in the same family showed bilateral microphthalmos.

(f) *Obesity, pigmentation of skin, retinitis pigmentosa, and meningocele.* Casini (1935) reports a markedly pigmented skin in the mother of five children, three of whom survived; two of these, both boys, were affected with an occipital meningocele and retinitis pigmentosa. The elder of these two boys was obese and had a skin pigmented like his mother's.

(g) *Gross malformation, obesity, and mental deficiency.* Two cases reported as examples of the Laurence-Biedl syndrome may possibly represent an allied, but independent syndrome. In both the fundi are reported as normal; the polydactyly was of an unusual type; and the other malformations were of a gross type. The familial factor was lacking.

1. Turner's (1931) case. Both hands showed imperfectly bifid thumbs as also rudimentary sixth fingers. There were six webbed toes on each foot, and extreme knock-knee with bilateral dislocation of the patellae. There was oxycephaly, a flattened forehead, 'almond eyes' and malformation of the teeth. Radiography showed flat and shortened middle phalanges of all fingers and toes, and defects in several epiphyses.

2. Livingston's (1937) case. The polydactyly consisted of two great toes on each foot, with two extra digits on each hand, one being in the usual post-axial position and the other springing from the base of the fourth finger. The left elbow was ankylosed, but the right showed undue mobility, a feature also shown by the fingers. The lower extremities were grossly disproportionate.

If there is a unity in this group it consists in the normal fundi, abnormalities of the thumbs or big toes, and possibly of the middle phalanges, in association with other gross defects, obesity, and mental deficiency. Hypogenitalism was not a prominent feature in any of the three cases. The negative features of normal fundi with positive and gross deviations from the typical picture of the Laurence-Biedl syndrome are therefore the essential characteristics in this group. As far as the skeletal changes are concerned, these cases suggest Apert's acrocephalosyndactyly.

(h) *The Stewart-Morel syndrome (obesity, intractable headaches, psychological disturbances, and internal frontal hyperostosis).* Though first clearly defined by Stewart (1927) the condition was known to Morgagni. There is no evidence that it is hereditary, and it is probably due to pituitary dysfunction. Most of the cases reported have come from mental hospitals and developed in adult life, sometimes quite late. Cranial hyperostosis is not always confined to the frontal bones, the parietal bones not infrequently also being involved. Bilateral optic atrophy from progressive ossification of the frontal bones in a woman aged 62 years has been reported by van Bogaert (1930). It is of interest to recall that frontal hyperostosis was present in the case of the Laurence-Biedl syndrome on which van Bogaert and Borremans (1936) reported post-mortem findings, and that a parietal osteoma was also present in the case of gigantism, mental deficiency, and retinitis pigmentosa reported by Böck and Risak (1934).

(i) *Hereditary apical dystrophy of hands and feet, associated with bilateral macular coloboma.* In a family reported by Sorsby (1935), the association of skeletal defects with a gross fundus lesion was noted in a mother and in five of her seven children. The presence of double thumbs in this group (but no post-axial polydactyly) is of interest in view of the occurrence of this

anomaly in the family with cerebellar ataxia, nystagmus, exophthalmos, and brachydactyly described by Biemond (1934), and in Turner's (1931) case of anomalous Laurence-Biedl syndrome. The absence of pre-axial hyperdactyly in other cases of the Laurence-Biedl syndrome is emphasized by their presence in other conditions. The dystrophy of the second phalanges in Amyot's (1937) case of the Laurence-Biedl syndrome is of interest in connexion with the similar changes seen in this group.

(j) *Adiposity, optic atrophy, ? mental deficiency.* During the past two years one of us (A. S.) has had the opportunity of examining three infants under the age of two years, who were abnormally fat, blind from optic atrophy, and apparently mentally deficient. No other obvious abnormalities appeared to be present, though unfortunately no detailed examination could be carried out in any of these cases. The parents were consanguineous in one case. The Wassermann reaction was known to be negative in two cases, and in one case the sella was found normal, radiographically. In one of these cases the mother was also abnormally fat, but her eyes were normal, as was her mentality. No definite history of difficult labour could be obtained in two cases; in the third prolonged and difficult labour was regarded as the cause of the child's condition. In two cases the child was an only child; in the third there were three other sibs who were said to be normal.

Whether these cases present a group of their own, or are examples of the incomplete Laurence-Biedl syndrome, cannot be definitely stated. The absence of pigmentary changes in the retina at this early age has no clear diagnostic significance, but the presence of fully established optic atrophy suggests a distinction from the Laurence-Biedl syndrome.

(k) *Syndactyly and retinal detachment.* An isolated case of the occurrence of bilateral retinal detachment in a non-myopic boy of 17 years, who showed syndactyly of his middle and ring fingers of both hands, is reported by Ochi (1938). In view of the familial incidence of both these components, the condition is worth noting in this discussion.

2. Genetics.

Streiff and Zeltner (1938) have dealt very fully with this in a recent paper and have published all the available pedigrees in full, so that there is no need to do more than summarize the facts and mention the different conclusions drawn from them. There are two main theories, the first is that one gene produces all the signs and that incompleteness of the syndrome is due to the action of modifying genes; the second is that the syndrome is determined by two or more genes. Supporters of the first view are Franceschetti (1936), van Bogaert (1938), and Stroesco (1936), and of the second Bauer (1927), Rieger and Trauner (1929), Ornsteen (1932), Savin (1935), and the authors of this paper. Rieger and Trauner (1929) think that both genes are recessive and lie in the same chromosome, one causing

the abnormalities of the ectoderm, and the other those of the mesoderm. Ornsteen (1932), however, believes that the association of the two genes is accidental, but agrees that one affects the development of the ectopic zone of the prosencephalon, from which the hypothalamus, infundibulum, optic chiasma, and retina take origin, and accounts for the obesity, genital

Table of Complete Sibships for Correction of Sex Ratio

| | 1 male 34:1 female 18. | | | | |
|-----------------|---|---------|----------------------|------------------|--------------------|
| Number with | 2 males 7:1 male and 1 female 8:2 females 1. | | | | |
| Laurence-Moon- | 3 males 2:2 males, 1 female 4:1 male, 2 females 2:3 females 1. | | | | |
| Biedl syndrome. | 4 males 0:3 males, 1 female 1:2 males, 2 females 2:1 male, 3 females 0:4 females 0. | | | | |
| | Male. | Female. | Percentage of males. | Secondary males. | Secondary females. |
| 1 | 34 | 18 | 65.3 | | |
| 2 | 22 | 10 | 68.7 | 11.5 | 4.5 |
| 3 | 16 | 11 | 59.3 | 10.1 | 7.9 |
| 4 | 7 | 5 | 58.3 | 5.0 | 4.0 |
| Total | 79 | 44 | 63 | 26.6 | 16.4 |

dystrophy, retinitis pigmentosa, and mental deficiency, and the other affects the mesoderm and accounts for the skeletal abnormalities. Macklin (1936) has suggested recently that there are two genes, one dominant and autosomal (lying in an ordinary chromosome), the other recessive and sex-linked (lying in the X-chromosome). She thinks that two recessive genes in an autosome cannot account for the high ratio of affected to normal children, or for the great excess of affected males.

Streiff and Zeltner (1938) deal with 88 fraternities, and the few additional records do not affect their arguments. In these there are 426 children, of whom 163 are affected, giving a ratio of 38.2 per cent. in place of the 25 per cent. expected of a recessive. The fact that parents who are heterozygous and have only normal children cannot be recognized, necessarily makes the ratio too high, and several methods of correcting this have been devised. Streiff and Zeltner (1938) give the corrected figures worked out by all the methods except Haldane's, and find that Weinberg's gives 30.4 per cent., Lenz's 28.1 per cent., Hogben's 27.3 per cent., and Weinberg's proband method 22.1 per cent. The theoretical figure lies between the highest and lowest of these. Macklin (1936), using a smaller number of fraternities corrects to 28.5 and thinks that 3.5 per cent. over the theoretical figure is significant, but Streiff, using Johannsen's calculation, shows that this is not so, and therefore Macklin's (1936) first objection is not valid. Her second objection that males are in excess (over 64 per cent.) makes her postulate the action of a sex-linked gene. Waardenburg has, however, pointed out that in the case of all rare recessives there is an excess of males. This is true if the published cases are accepted as a true index of the ratio, but males are more likely than females to come under observation, and Haldane (1938) has shown by an ingenious calculation that in albinism, where males form more than 54 per cent. of the recorded cases, there is probably no real inequality of the sexes.

Complete Sibship

| | Number of pregnancies. | ♂ | ♀ | • | ♂ | ♀ | ○ | Consanguinity. | Remarks. |
|---------------------------|------------------------|---|---|---|---|---|---|----------------|---|
| Amyot | 11 | — | 1 | — | 4 | 2 | — | — | 4 O died in infancy |
| Arena | 8 | — | 1 | — | 3 | — | — | — | 3 miscarriages 1 died at 18 years, of congenital heart disease 1 died soon after birth |
| Becker | 4 | 1 | — | — | — | 2 | 1 | — | — |
| Biernond (family A) | 1 | — | 1 | — | — | — | — | — | 4 ♂ and 2 ♀ died without issue; ♀ dead; retinitis pigmentosa and polydactyly. |
| Biernond (family X) | 13 | 2 | 1 | — | 1 | 2 | — | — | 1 abortion; O died at 2 years, from 'pulmonary disease', and had polydactyly. |
| Bietti (Case 2) | 6 | 1 | — | — | — | — | 3 | None | 1 abortion at 5 months, had polydactyly |
| Bietti (Case 3) | 3 | 1 | — | — | — | 1 | — | None | — |
| Carrau and Echeverry | 1 | 1 | — | — | — | — | — | — | ♀ died at 12 years, had 12 fingers and 12 toes, poor vision, and Fröhlich's syndrome |
| Copperstock | 13 | 1 | 1 | — | — | — | 6 | — | ♂ died at 13 months, obese, polydactyly ♂ died at 3 days, obese, polydactyly 2nd pregnancy, premature twins, ♀ died |
| Franceschetti and Streiff | 5 | 1 | — | — | — | 1 | — | 1st cousins | 3 ♂ died young, one had polydactyly |
| Gabriélides | — | 1 | — | — | 2 | 1 | — | None | — |
| Giannini | 3 | — | 1 | — | 2 | — | — | — | — |
| Gillespie | 5 | 1 | — | — | 1 | 1 | — | None | 2 stillbirths O at full term |
| Hayashi | 3 | 1 | — | — | — | — | 2 | Yes | — |
| Hutton | 3 | 2 | 1 | — | — | — | — | None | — |
| Jenkins and Poncher | 6 | 1 | — | — | 2 | — | — | — | 1st pregnancy, spontaneous abortion at 2 months 2nd, twin boys, died at 6 months, 'nutritional disturbances', 3rd, ♀ died soon after birth, defect of spinal cord |
| Klenerman | 4 | — | 1 | — | — | 3 | — | None | A stepbrother normal |

Maldonado

6 1 — — — 5* 2nd cousins

* One of these, a girl aged 14 years, is stout

| | 4 | — | 1 | — | 3 | — | 5* | 2nd cousins | |
|-------------------------------------|-------------------------|-------------|-------------|-------------|--------------|-------------|-------------|------------------------------|---|
| Maldonado | 6 | 1 | — | — | — | — | — | — | * One of these, a girl aged 14 years, is stout |
| Molitch, Gladen, and Pigott | 13 | 3 | — | — | 1 | 5* | — | None | ♀ died at 20 years, of appendicitis ♀ died at 1 year, ♀ died at 2 years; 'worms', ♀ died at birth * one is a moron |
| Mutch | 5 | 1 | — | — | 3 | 1 | — | None | — |
| Paton | 4 | 2 | — | — | 1 | 1 | — | — | — |
| Ricci | (a) 3 (b) 7 (c) 5 | 1 1 1 | — — — | — — — | 1* — — | — — — | 1 5 2 | None None None None | * M.D. atypical retinitis pigmentosa 1 miscarriage 2 miscarriages ♀ died at 18 months, extra fingers and toes ♂ died at 3 years, obese, backward, and extra toes 1 died at 4 years, encephalitis, syndactyly of hands, and extra toes both feet. 1 abortion The 3 affected children are deaf mutes * 6 ♂ died young ♂ died at 4 months, 'meningitis after scarlet fever' |
| Savin | 8 | 1 | — | — | 2 | 3 | — | None | 2 brothers (only survivors) dwarfed; 4 premature births, died early; O died at 2 years Mother married a second time—healthy child |
| Spektor and Sokolov | 5 | 1 | — | — | 1 | 1 | — | Yes (uncle-niece) | Parents Egyptian. The father married a second time; the 3 children (1 boy 2 girls) of this marriage are normal 2 ♂ died at 10 and 4½ years; * 1 of these died recently from pneumonia at 23 years 2 miscarriages 1 ♀ died at 3 weeks |
| Steinberg | 5 | — | 3 | — | 1 | 1 | — | Cousins | — |
| Uyeno | 11 | — | 1 | — | — | — | 10* | Yes | — |
| Van Bogaert and Borremans | 5 | 2 | — | — | 1 | 1 | — | — | — |
| Villegas | — | 1 | — | — | — | — | 2 | None | — |
| Warkany, Frauenberger, and Mitchell | 8 | — | 1 | — | — | — | — | — | — |
| Weissberg | 1 | — | 1 | — | — | — | — | None | — |
| Yamamoto | 1 | — | 1 | — | — | — | — | None | — |
| Zaky | 4 | 1 | — | — | 1 | 2 | — | None | — |
| Present series | (a) 5 (b) 11 | 2* 1 | — 1 | — 1 | 1 — | — 6 | — — | 1st cousins 1st cousins | — |
| Total | 33 | 16 | 0 | 28 | 34 | 37 | | | |

♂ = affected male. ♀ = affected female. ● = affected, sex unstated. ♂ = normal male. ♀ = normal female. O = normal, sex unstated

The method is based on the assumption that in the fraternities with two or more affected, the probands were in the same sex ratio as in those containing one. Using the method for the Laurence-Moon-Biedl syndrome, there is almost as great an excess of secondary males over secondary females as in the total of recorded cases in complete fraternities, instead of the number being nearly equal as in albinism. Though the numbers are small this does suggest that there is a true excess of males (see Table of Complete Sibships for Correction of Sex Ratio on p. 61).

Apart from this, there is a fatal objection to Macklin's (1936) theory. It requires that there should be five times as many fraternities with only males affected, as with both males and females affected, but actually there are nine with two or more affected males and 17 with affected children of both sexes.

Sex ratio. In the full sibships the ratio of males to females is 79 : 44 with 3 of unstated sex, and there were amongst the infants who died probably 8 males, 6 females, and 4 of unstated sex. Taking all sibships the ratio is 112 : 62 so that males form rather more than 64 per cent. of those affected.

Consanguinity. The complete sibships give the most reliable figures, and of these there are 50 in which there is definite information about the presence or absence of consanguinity in the parents. Of these 10 were the offspring of first cousins, 4 of second cousins, 1 of cousins, 1 of uncle and niece, and 3 of blood relations; in the remaining 31 the parents were unrelated by blood, so that 20.4 per cent. were the result of marriages between first cousins and 38.7 per cent. were the result of consanguineous marriages. There are also 31 sibships about whose parents no statement is made, and if these are counted as unrelated, 12.3 were the result of marriages between first cousins and 23.4 were the result of consanguineous marriages.

Among the 72 incomplete pedigrees, the parents were: first cousins 1, uncle and niece 1, cousins 1, consanguineous 1, doubtful 1, and unrelated 4. This high rate of consanguinity, and in particular of first cousin marriages, is characteristic of a rare recessive.

In the case of rare recessives it is unusual for a parent with the condition to have an affected child, and we pointed out in our former paper that in the case of this syndrome there was no recorded instance of direct transmission from parent to child. Van Bogaert and Delhay (1936) have, however, recorded a family in which the mother of two affected children had herself retinitis pigmentosa and mental abnormality. Although the author thinks this is in favour of dominant inheritance, it is more probable that the mother was a homozygous recessive and married a heterozygote. The expectation in such a marriage is that half the children will be affected and half normal, an expectation that was fulfilled in this case.

The large number of ascendants and collaterals with obesity, abnormalities of the skeletal system, or some other incomplete expression of the syndrome, shows that it is not always completely recessive and that heterozygotes are sometimes recognizable.

The strange combination of ectodermal and mesodermal defects makes it

more likely in our opinion that two recessive genes in the same chromosome determine the syndrome, or that it is dependent on some chromosome error such as a dislocation or translocation, than that a single gene substitution is responsible. The variability of the manifestations found in those affected is probably due to the action of modifying genes.

Our suggestion in a former paper that the same recessive mutation in two neighbouring genes was unlikely to happen more than once, and that all cases probably had a common origin seems much less likely since the Japanese cases have been recorded, but the same chromosome error, such as dislocation, might well occur on more than one occasion, and for this reason seems more probable than a double gene mutation.

Incomplete Sibship

| | ♂ | ♀ | • | Consanguinity. | Remarks. |
|--------------------------|----|---|---|-------------------------|--|
| Aschner | 1 | — | — | Yes: Cousins | A sister had polydactyly |
| Aschner and Kornfeld | 1 | 1 | — | — | — |
| Bietti (Case 3 b) | 1 | — | — | — | Seven brothers all healthy |
| Boros | 1 | — | — | — | — |
| Dods | 1 | — | — | — | — |
| Frank | 1 | — | — | — | — |
| Groos | — | 1 | — | None | — |
| Gurich | — | 1 | — | — | — |
| Judge | 1 | — | — | Yes | — |
| Klenerman | — | 1 | — | — | — |
| Lhermitte and Bollack | — | 1 | — | — | One half-brother epileptic, another had spinal bifida |
| Loepp | 1 | — | — | Yes: uncle and niece | — |
| Marks | 1 | — | — | — | — |
| Pesme and Hirtz (a) | 1 | — | — | None | A sister at 8 years stout |
| (b) | — | 1 | — | — | Two younger sibs normal |
| (c) | 2 | — | — | None | — |
| Roger and Farnarier | 1 | — | — | — | — |
| Rovinsky | — | — | 1 | — | Oxycephaly |
| Smith | 1 | — | — | — | — |
| Steinberg | 1 | — | — | — | Deaf mute |
| Van Lint and van Bogaert | 2 | — | — | — | — |
| Weekers | 1 | — | — | None | — |
| Total | 18 | 6 | 1 | | |

♂ = affected male. ♀ = affected female. • = affected, sex unstated

Summary

1. Analysis of case reports in the literature shows the frequent occurrence of one or more components of the Laurence-Biedl syndrome in the ascendants of patients showing the full syndrome. No case of the inheritance of the full syndrome is known, though cases are reported indicating that patients exhibiting the syndrome are not sterile.

2. The literature also reveals that the condition is not confined to the Caucasian race.

3. The available post-mortem studies have not shown any characteristic lesions.

4. Of interest in the new cases reported here, is the observation that one previously obese patient is now distinctly thin.

5. Attention is drawn to a series of allied conditions.

6. It is suggested that the syndrome is determined by two recessive genes in the same chromosome, or that it is dependent on some chromosome error such as a dislocation or translocation.

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SUBSTITUTION THERAPY IN HYPOPITUITARISM¹

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Introduction

With Plate 3

It has often been shown that if the pituitary gland is removed, the gonads and the thyroid gland atrophy, and the basal metabolism falls. The administration of anterior pituitary extracts repairs these deficiencies, but if the extracts are obtained from a different species, the glands return to their original state after a certain period of time, in spite of continued injections. As a result, the basal metabolic rate after its initial rise falls to a level as low as that of the hypophysectomized animal. Anderson and Collip (1934) were the first to show that the serum from a horse or from rats, which had received daily injections of thyrotropic extract of the anterior pituitary for some weeks, depressed the metabolism of normal rats, and prevented the rise in metabolism of normal and hypophysectomized rats which received at the same time injections of thyrotropic extract. Scowen and Spence (1934, 1936) observed that the serum of rabbits, similarly treated with ox thyrotropic extract, prevented ox thyrotropic extract from producing thyroid hyperplasia in guinea-pigs. These effects are attributed to antithyrotropic substances, or so-called antihormones.

In normal men and in patients with pituitary insufficiency caused by pituitary tumours, the response to thyrotropic extract over short periods is similar to that of animals, in that a considerable increase in the basal metabolic rate is produced through stimulation of thyroid activity (Lederer, 1935; Scowen, 1937). In this communication we record the results obtained when two patients with pituitary insufficiency were treated with thyrotropic extract for many weeks, and we show that in man also a refractory state develops.

Case Reports

Case 1. Hypopituitarism after removal of chromophobe adenoma. A man, aged 59 years, had been under the care of Professor J. Paterson Ross thirteen months previously, when a chromophobe adenoma of his pituitary was removed because of failing vision. Five months after the operation he began to suffer from spasms of twitching of his legs, lasting about three hours, and from stiffness of his legs, which became so great that it was difficult for him to rise from a sitting position. Except for loss of appetite and loss of weight, there were no other complaints.

¹ Received October 13, 1933.

On examination. He was tall and thin, somewhat drowsy and apathetic, taking little interest in his surroundings. His temperature varied from 97° to 98° F., the pulse from 60 to 70. The skin was pale, scaly, and dry; the hair on his head was scanty; he thought that his baldness had increased during the previous year; the outer half of the eyebrows was absent; and the pubic and axillary hair scanty. The tongue showed slight atrophy of the papillae, with smooth edges and tip. The thyroid was not palpable. The eyes showed a left ptosis, the pupils were normal, there was weakness of the left internal rectus; the disks were pale; and the visual fields showed bitemporal hemianopia. The arms were thin, but otherwise normal. The legs were partially extended and crossed, with marked rigidity, especially of the adductors; the sensation and reflexes were normal.

Fractional test meal. Achlorhydria, but a slight secretion of HCl after the subcutaneous injection of 0.5 mg. of histamine.

X-rays of stomach. The gastric rugae appeared to be considerably narrowed and flattened, and there were very few transverse or oblique rugae along the greater curvature.

Gastroscopy (Dr. F. Avery Jones). Atrophic gastric mucosa.

Basal metabolic rate. Varied from -3 to -21 per cent.

Blood. Cell count normal, except for a slight anaemia; Wassermann reaction negative; serum-calcium, plasma-chloride, serum-sodium, blood- and serum-cholesterol, blood-urea and alkali reserve within normal limits.

Treatment and progress. Before treatment was begun, the patient was observed for two weeks, and three readings of the basal metabolic rate were made. He was then given daily intra-muscular injections of 1 c.c. of extract of pig pituitary containing 400 Heyl-Laqueur units of thyrotropic hormone. The supply of this particular extract was exhausted after seven weeks, and he was then given instead 2 c.c. of ambinon (extract of pig pituitary containing about 200 Heyl-Laqueur units of thyrotropic hormone and 50 units of gonadotropic hormone per c.c.). One month after treatment with thyrotropic hormone was started, he was given in addition 500 rat units of pregnyl (gonadotropic extract of human urine of pregnancy) intramuscularly three times a week.

Effect on B.M.R. During the first ten days of treatment with thyrotropic extract there was no appreciable change in the basal metabolic rate. Three days later it rose from -16 to +13 per cent., and after a further two days to +57 per cent., an unreliable figure owing to restlessness during the test. Thereafter the basal metabolic rate fell; on the thirtieth day after the first injection it was -17 per cent., and on the fifty-fifth day it was as low as -43 per cent. A low level of basal metabolism was maintained in spite of continued injections of thyrotropic extract (Fig. 1).

On the forty-seventh day after treatment was begun, blood was withdrawn from the patient to determine whether the serum possessed anti-thyrotropic properties. Five female guinea-pigs, each weighing about 200 gm., were injected daily for five days with 2 c.c. of serum intraperitoneally, and 4 Heyl-Laqueur units of thyrotropic extract subcutaneously. Five female guinea-pigs of similar weight were given daily subcutaneous injections of 4 Heyl-Laqueur units of thyrotropic extract alone for five days. On the

sixth day the animals were killed. The thyroid glands of all the control guinea-pigs were nearly twice the normal size, and histologically showed marked hyperplasia; those of the guinea-pigs which received serum in addition to thyrotropic extract were normal in size and histological appearance, showing that the serum contained a substance which inhibited the action of thyrotropic hormone (Table I, Plate 3).

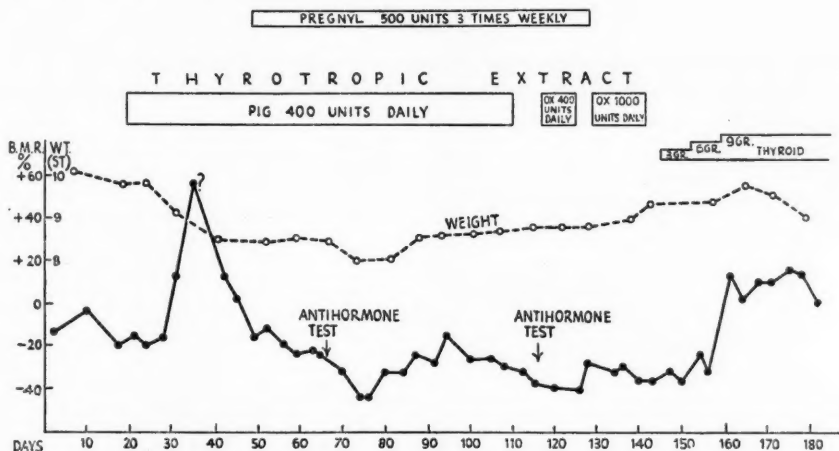


FIG. 1. Effect of daily injections of thyrotropic extract on the B.M.R. in hypopituitarism (Case 1).

Rowlands (1938), among others, has shown that antisera to various gonadotropic extracts may possess a specificity according to the species of animal (species-specificity) or source in the body (source-specificity) from which the extract was prepared; some antisera, e.g. antisera to gonadotropic extracts of human urine of pregnancy and pregnant mare serum, may show complete species-specificity, others, e.g. antisera to gonadotropic extracts of pituitary origin, may exhibit only incomplete species-specificity. Thus the serum of rabbits injected with gonadotropic extracts of ox pituitary possessed incomplete species-specificity, in that it did not inhibit the effects on immature rats of gonadotropic extracts of sheep and pig pituitary, but inhibited gonadotropic extracts of human pituitary, horse pituitary, and pregnant mare serum.

To determine whether the antiserum which had been obtained to thyrotropic extract of pig pituitary in this patient would inhibit thyrotropic extract from a different species, Dr. Rowlands kindly assayed the serum against a thyrotropic extract of ox pituitary. It will be seen (Table II) that its power to inhibit pig thyrotropic extract was great—as little as 0.4 c.c. of serum almost completely inhibited the action of 1 mg. (10 Heyl-Laqueur units) of pig thyrotropic extract—and that it also inhibited, but to a lesser extent, thyrotropic extract of ox pituitary. This inhibition of ox thyrotropic extract, however, was sufficient to prevent a rise in the basal metabolic

rate when ox thyrotropic extract was administered to the patient. At first, daily injections of 400 Heyl-Laqueur units of ox thyrotropic extract were given, and at the end of one week this dose was increased to 1,000 units daily, and maintained for thirteen days without causing any rise in the basal metabolic rate. Thereafter, he was given 3 gr. of thyroideum siccum daily, and since there was no change in the basal metabolic rate at

TABLE I

Showing the Inhibition of Thyrotropic Extract Injected into Guinea-pigs by the Serum of a Patient (Case I) Injected with Thyrotropic Extract for a Prolonged Period.

| Number of guinea-pig. | Thyrotropic extract. | Serum. | Body-weight in gm. | Thyroid weight in mg. | Hyperplasia. | Remarks. |
|-----------------------|---------------------------|-------------------------|--------------------|-----------------------|--------------|---|
| 505 | 4 units daily for 5 days. | Nil | 223 | 52 | ++ | Average body-weight, 213 gm. Average thyroid weight, 52mg. Increase above normal thyroid weight, 20 mg. |
| 506 | " | " | 197 | 57 | ++ | |
| 507 | " | " | 215 | 57 | ++ | |
| 508 | " | " | 217 | 49 | ++ | |
| 509 | " | " | 216 | 45 | ++ | |
| 510 | " | 2 c.c. daily for 5 days | 240 | 30 | — | Average body-weight, 218 gm. Average thyroid weight, 29mg. Decrease below normal thyroid weight, 4 mg. |
| 511 | " | " | 224 | 32 | — | |
| 512 | " | " | 211 | 28 | — | |
| 513 | " | " | 211 | 25 | — | |
| 514 | " | " | 203 | 30 | — | |

TABLE II

Showing the Inhibition of Thyrotropic Extract by the Serum of Case 1 (Data of Dr. I. W. Rowlands). (The Figures are the Average Obtained in 10 Guinea-pigs in each Group. Injections were given Subcutaneously. 1 mg. of Thyrotropic Extract is Equivalent to about 10 Heyl-Laqueur Units.)

| Source of extract. | Dose of thyrotropic extract. | Dose of serum. | Body-weight of guinea-pigs in gm. | Weight of thyroids in mg. | Increase of thyroid weight above normal in mg. |
|--------------------|------------------------------|---------------------------|-----------------------------------|---------------------------|--|
| Pig | 1 mg. daily for 5 days | Nil | 194 | 62 | 31 |
| " | " " | 0.4 c.c. daily for 5 days | 180 | 35 | 3 |
| Ox | " " | Nil | 187 | 65 | 36 |
| " | " " | 0.4 c.c. daily for 5 days | 190 | 50 | 21 |

the end of a week, the dose was raised to 6 gr. daily. After four days the basal metabolic rate was still at the low level of - 32 per cent. When the dose was increased to 9 gr. daily, there was a prompt rise of the basal metabolism.

Effect on general condition. After the patient had received thyrotropic extract for one week, he developed an irregular fever, with occasional rigors and vomiting, which persisted for two weeks. He was then more or less afebrile for two weeks, but developed an irregular fever again after a further two weeks; thereafter, he remained afebrile, except for very occasional rises of temperature to 100° and 101°F. The cause of the fever was un-

explained, unless it was a reaction to the foreign proteins of the extract. The rise in metabolism was not thought to be the result of the fever, as fever was also present when the metabolism was low.

The adductor spasms, which caused so much discomfort, greatly diminished in frequency and severity after one week's treatment with thyrotropic extract, and after two weeks disappeared entirely. Whereas before treat-

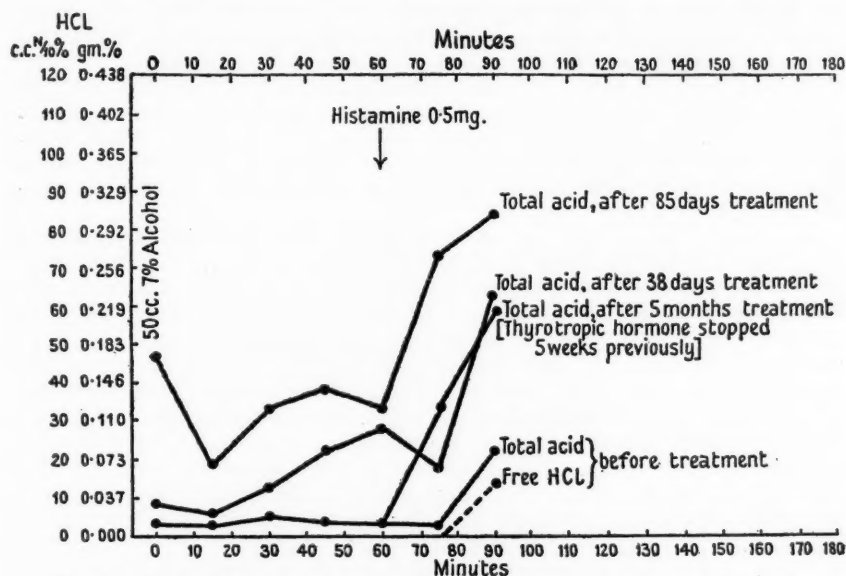


FIG. 2. Showing the effect of thyrotropic and gonadotropic extracts on gastric secretion (Case 1).

ment he was lethargic and disinclined to talk or exert himself, during treatment he became much brighter and more cheerful, and after three months spent the afternoons in walking in the hospital square. When the administration of thyrotropic extract was discontinued, his mental state remained cheerful, but his adductor spasms returned within two weeks. They were unrelieved by pregnyl, pituitrin, or thyroideum siccum, but were relieved again by the subsequent administration of thyrotropic extract. The specific effect of thyrotropic extract on these muscular cramps is unexplained.

The condition of his skin remained unchanged. His weight during the first ten weeks gradually fell from 10 to 8 stone, possibly due to the vomiting, but during the next three months it gradually rose to its previous level.

Effect on gastric secretion. During treatment with thyrotropic and gonadotropic extracts, a fractional test meal showed an increased secretion of acid, instead of the previous achlorhydria, and later during treatment the increase of acid secretion was considerable (Fig. 2). Gastroscopy at this time showed that the gastric mucosa was hyperaemic and apparently

regenerating. After treatment with thyrotropic and gonadotropic extracts was stopped, achlorhydria returned.

Case 2. Hypopituitarism after resection of suprasellar cyst. A man, aged 20 years, had begun to suffer from bilateral frontal headaches, nausea, and vomiting at the age of 10, and four years later from disturbance of vision. His height at the age of 14 years was 4 ft. 9 in., and there was little subsequent growth. He became increasingly obese round the lower part of the trunk, and at 16 years became subject to transitory bouts of temper. Puberty did not take place; he grew no hair on his face or body, and developed no sexual interest; his genitalia remained infantile. He had previously been an active boy, interested in games, but from this time he became placid, slow in his movements, and mentally rather sluggish. Nevertheless, his mental development was normal, he won a scholarship, and later worked efficiently as a clerk. At the age of 18 years, his testes, which until then were said to have been undescended, descended spontaneously.

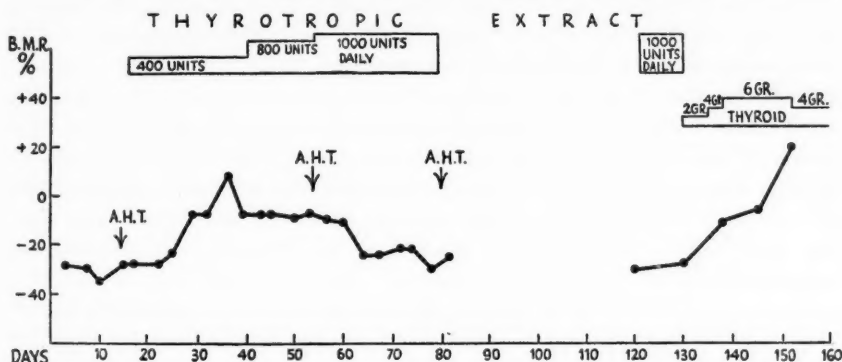
On examination at the age of 19 years, he was somewhat drowsy and sluggish. His height was 4 ft. 9½ in. and weight 6 stone. The voice was high pitched; there was excess of fat under the chin and on the chest and abdomen; the configuration of the body was feminine in type. The skin was dry; the hair on his head normal, but the eyebrows were scanty and he was elsewhere hairless. The eyes showed rotatory nystagmus on looking upwards; there was some weakness of the right superior rectus, and the left pupil was slightly larger than the right. In the optic fundi the vessels were engorged, and there was optic atrophy. The visual fields showed bitemporal hemianopia. The tongue and teeth appeared normal. The thyroid was not palpable. The penis was infantile, the scrotum retracted, the testes small and retractile, and the prostate small. Voice (report of Mr. F. C. W. Capps): very nearly adult range, larynx small and infantile in type. The development of the epiphyses of the phalanges, wrist, and elbow corresponded to about the age of 14 years. The epiphysis of the lesser trochanter of the femur was just forming. The cortical layer of the long bones was thin and not as dense as normal. The basal metabolic rate was -19 per cent. The glucose tolerance curve and the blood count were normal.

Craniotomy was performed by Professor J. Paterson Ross, and a large suprasellar cyst partially resected. Eight months later, his general condition had remained unchanged. His height was then 4 ft. 9½ in. and weight 6 st. 5 lb. His visual fields had slightly increased in size. There was no alteration in the X-ray appearances of his pituitary fossa and epiphyses. The glucose tolerance curve, fractional test-meal, blood count, serum-calcium, and blood-cholesterol were within normal limits. The basal metabolic rate was -27 per cent.

Treatment and progress. The patient was treated first with thyrotropic extract. Before treatment, four preliminary readings of the basal metabolic rate were made and it was found to vary from -27 to -34 per cent. His serum, injected into five guinea-pigs in doses of 2 c.c. daily for five days, did not inhibit the action of thyrotropic extract injected in daily doses of 10 Heyl-Laqueur units for the same period.

He was then given daily intramuscular injections of 400 units of thyrotropic extract. On about the ninth day his basal metabolic rate began to

rise, on the fourteenth day it was -8 per cent., and on the twenty-first day $+8$ per cent. Three days later the basal metabolic rate fell to -8 per cent., and remained at this level for three weeks, in spite of double the dose of thyrotropic hormone (Fig. 3). An 'antihormone' test, in which 1 c.c. of serum and 10 units of thyrotropic hormone were used, failed to reveal any evidence of antithyrotropic activity in his serum. On increasing the dose



A.H.T. = Antihormone test

FIG. 3. Effect of daily injections of thyrotropic extract on the B.M.R. in hypopituitarism (Case 2).

of thyrotropic extract to 1,000 units a day (5 c.c. of ambion, the supply of the original thyrotropic extract being now exhausted), the basal metabolic rate fell to -25 per cent., but serum tested when the basal metabolic rate was at this level, after treatment for sixty-six days, again failed to inhibit the action of thyrotropic extract in guinea-pigs. There was no change in the patient's clinical condition while he was receiving this treatment.

Treatment was then stopped and the patient discharged for five weeks. On re-admission, he was given intramuscularly 5 c.c. of ambion (1,000 units of thyrotropic hormone and 250 units of gonadotropic hormone) for nine days, with no change in his basal metabolic rate, which remained at -25 per cent. He was then given thyroideum siccum by mouth in doses of 2 gr. daily, and five days later, 4 gr. daily. Three days after this the basal metabolic rate rose to -11 per cent. Seven days after increasing the dose to 6 gr. daily, the basal metabolic rate was -6 per cent., but after a further seven days $+20$ per cent., whereupon the dose was reduced to 4 gr. a day. Later, still further reduction in dose was necessary. With the increase in metabolism, there was a considerable improvement in mental outlook.

Discussion

In response to thyrotropic extract the basal metabolic rate in these two patients behaved in the same way as in the lower animals—a transitory rise and a subsequent fall to a low level in spite of continued treatment. These

findings suggest that the clinical usefulness of thyrotropic extract is likely to be limited, and that if it be employed, it should be confined to periods of three weeks with alternating rest periods. Our first patient demonstrates that in man, as in the lower animals, after prolonged treatment with thyrotropic extract from a different species the blood-serum may acquire the power of inhibiting the action of the thyrotropic hormone.

The second patient failed to develop any inhibitory property in his serum, although the basal metabolic rate followed a curve similar to that of the first patient. This could not have been due to lack of potency of the extract, for the initial increase in basal metabolism was obtained, and in the 'antihormone' test, in which the same material was used, the thyroid glands of the animals were almost doubled in weight. We are unable to explain why antihormone was not produced in this patient, or why in the absence of antihormone the basal metabolism should fall. It may be that the thyroid had been atrophic for so long that it was unable to maintain a response to the stimulus.

It is noteworthy that in both patients there was a considerable latent period before the metabolism began to rise, in the first patient ten days, in the second about nine days. In normal men the basal metabolic rate begins to increase within twenty-four to forty-eight hours after administration of thyrotropic hormone. The delayed response in our patients may be related to previous atrophy of the thyroid; on the other hand, in view of the large doses of thyroid subsequently required to raise the metabolism, it may be due to some intrinsic disturbance of the body cells. In the lower animals, antithyrotropic serum does not inhibit the action of injected thyroxine (Anderson and Collip, 1934).

Of interest is the remarkable effect of thyrotropic extract on the cramps, which were a prominent symptom in the first patient. These cramps appeared to be unrelated to the serum-sodium, plasma-chloride, and serum-calcium, which were present in normal amount. The disappearance of achlorhydria in this patient and its replacement by a high level of acid secretion during treatment with pregnyl and thyrotropic extract, and the re-appearance of achlorhydria on stopping this therapy were equally striking. These findings, together with the occurrence of achlorhydria in Simmonds' disease and in the syndrome of anterior pituitary insufficiency associated with anaemia and subacute combined degeneration described by Snapper, Groen, Hunter, and Witts (1937), lead one to speculate whether the gastric mucosa is under the control of the anterior pituitary.

It is noteworthy that the development of resistance to the metabolic effects of pituitary extract was associated with the maintenance of improvement in the musculature and the stomach. In general we must regard the effects of substitution therapy in pituitary disease as disappointing, but there is sufficient evidence to suggest that not all aspects of the activities of the hormones are blocked by antihormones, and that some beneficial action persists.

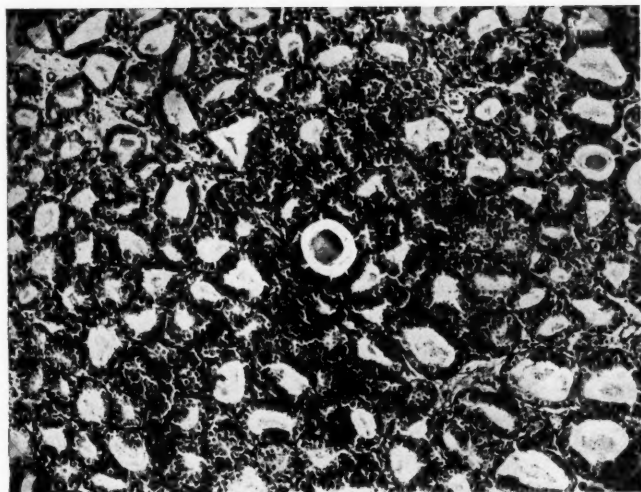
Summary

Two men with hypopituitarism after operations for pituitary tumour were treated with thyrotropic extract for a prolonged period. As in the lower animals, the basal metabolic rate responded by a rise, followed by a fall to the previous low level in spite of continued treatment. The blood-serum of one patient inhibited the action of thyrotropic extract injected into guinea-pigs; antithyrotropic properties could not be demonstrated in the serum of the other. In both patients the basal metabolic rate subsequently rose on the administration of thyroid, but large doses were necessary. During treatment with thyrotropic and gonadotropic hormones, there was a great increase in the gastric secretion of free HCl in one patient who had had achlorhydria, and the gastric mucosa, which before treatment was atrophic, appeared through the gastroscope to be regenerating.

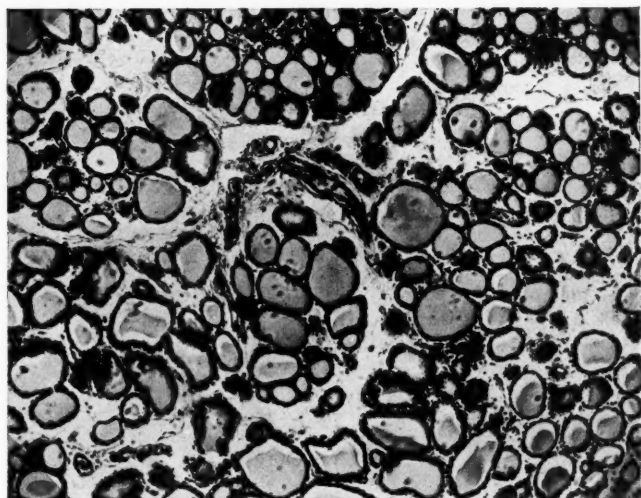
We wish to thank Dr. A. N. Macbeth, of Organon Laboratories, for generous supplies of thyrotropic extract, ambinon, and pregnyl, and Dr. A. S. Parkes for the ox thyrotropic extract.

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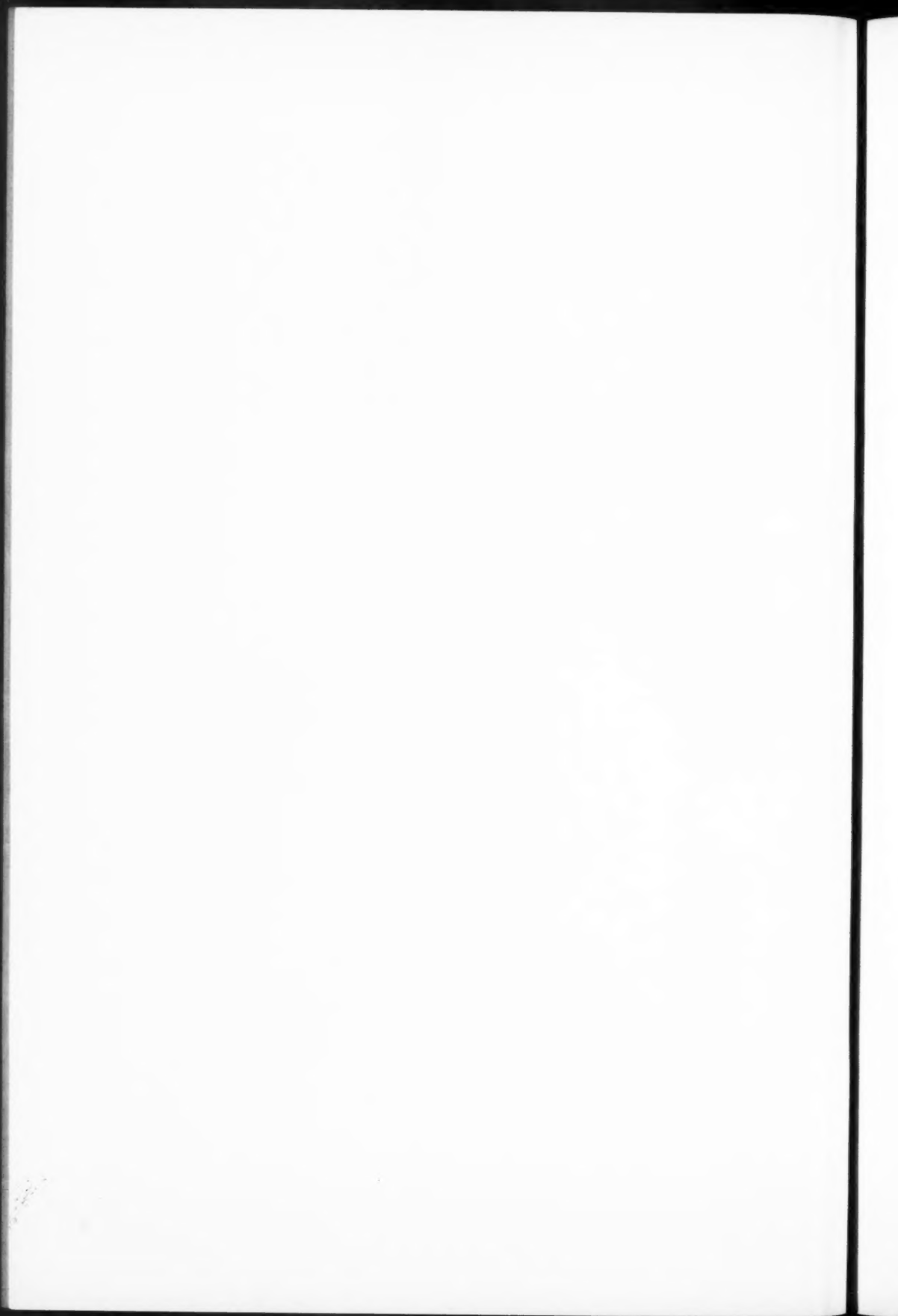
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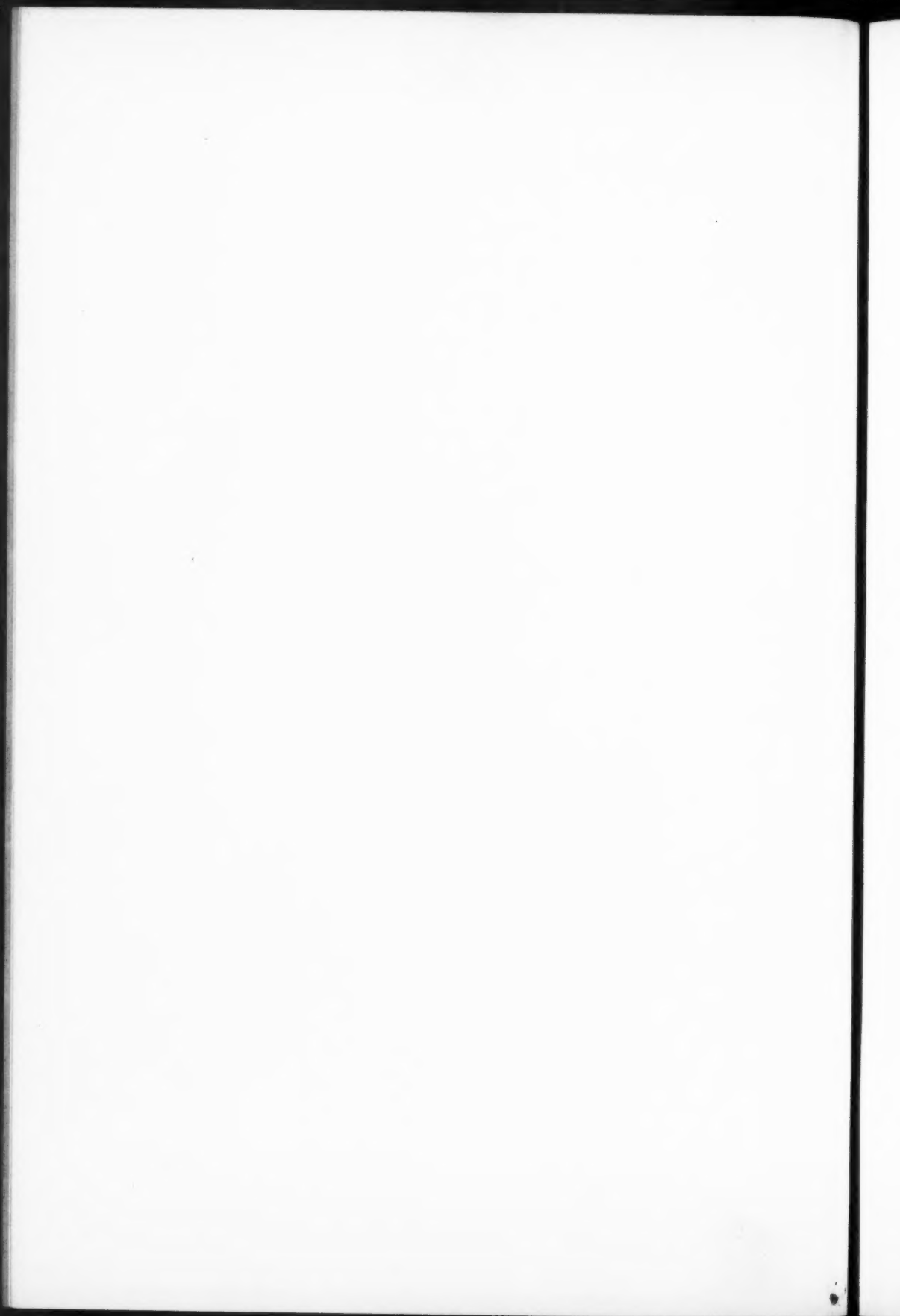
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a. Photomicrograph of section of guinea-pig 508, which received daily injections of thyrotropic extract only for 5 days.

b. Photomicrograph of section of thyroid of guinea-pig 514, which received, in addition to thyrotropic extract, 2 c.c. of serum from Case 1 daily for 5 days, showing inhibition of the action of thyrotropic hormone.







BENIGN BRONCHO-PULMONARY INFLAMMATIONS ASSOCIATED WITH TRANSIENT RADIOGRAPHIC SHADOWS¹

By HUGH RAMSAY AND J. G. SCADDING

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Department of Medicine, British Postgraduate Medical School)

With Plates 4 to 6

Introduction

THE increasing use of radiological examination in the diagnosis of inflammatory diseases of the respiratory tract has shown that a variety of radiological opacities in the lung fields, often transitory, may occur in the course of such diseases, without the grave symptoms associated with the generally recognized forms of pneumonia. Certain varieties of these opacities have attracted much attention recently, and have been described under the title of 'pneumonitis' (Allen, 1936; Gill, 1938; Maxwell, 1938). It has been the experience of both of us, one in a tuberculosis clinic, the other in a general hospital, that the association of respiratory infections of a clinically benign nature with definite radiological changes in the lungs is comparatively common. It seemed that an analysis of cases of this sort would be useful, and in order to present a concept of the relative frequency of the conditions to be described, we have confined our analysis to the cases seen by one of us (H. R.) at the Walthamstow Tuberculosis Dispensary during the past two years. In view of the fact that this clinic offers convenient clinical and radiological facilities for diagnosis in the vicinity of the patients' homes, it is probable that those suffering from the more benign conditions are more frequently subjected to radiological examination than is possible in less favourable circumstances. The records of this Dispensary over the period March 1936 to February 1938 were searched for cases in which ambulant patients presented symptoms suggestive of a respiratory infection accompanied by localized shadows in the radiogram of the lungs which further observation showed to be transient. Cases of abnormal accentuation of the linear striations were not included. Twenty-nine such cases were found out of a total of 1,220 new cases seen. They fall into the following three groups:

- I. Delayed resolution of acute pneumonia, four cases.
- II. Lobar atelectasis without acute symptoms, four cases.
- III. Twenty-one cases not falling into either of the above groups.

¹ Received November 4, 1938.

Of these, the first two groups, having a well-recognized pathological basis, will be discussed only briefly; group III needs fuller discussion.

Cases

Group I. Delayed resolution of acute pneumonia. Four of the cases fell into this group; in each there was a history of persistent symptoms after recovery from an acute illness, severe enough to have been a frank pneumonia. It is probable that the number of cases in the present series falling into this group is relatively small, because it is only if symptoms persist for an unusually long time after acute pneumonia that the patient is likely to be referred to a tuberculosis clinic. The shadows observed in this group were essentially similar to those described below as occurring in the cases of group III, and only the history of a preceding acute phase determined the diagnosis. It is agreed by all who have made radiological studies of pneumonia that resolution may be much delayed and yet eventually be complete. Thus with regard to pneumococcal lobar pneumonia, Graesar, Wu, and Robertson (1934) record such delay for eighty-five days, and Davies, Hodgson, and Whitby (1935) for seventy-two days; and slow resolution has been noted to occur in some of the pneumonias associated with influenza (Scadding, 1937 a).

Group II. Lobar atelectasis. Four cases in the series showed radiological appearances characteristic of left lower lobe atelectasis. One of these is shown in Plate 4, Figs. 1 and 2. The triangular basal shadow, overlapped by the heart if on the left side, or beside the heart-shadow if on the right, with displacement of the heart to the affected side and elevation of the corresponding side of the diaphragm, is well recognized to be pathognomonic of atelectasis (Bowen, 1929; Manges and Farrell, 1935). There is good evidence that similar triangular shadows, even without displacement of the mediastinum and diaphragm, about which there has been in the past much controversy, also represent atelectatic lower lobes (Anspach, 1934); in these cases, which are commoner in children, there is presumably more perfect compensatory emphysema of the remainder of the ipsilateral lung. These four cases all presented symptoms of bronchitis—cough and sputum—for several weeks before their first attendance. None of the patients gave a history of an acute sudden onset, though they had been ill enough to rest at home, and in two cases to be confined to bed for a few days. Two occurred in children, aged 9 and 11 years respectively, and two in young adults. The case of the younger child is of especial interest in that transient collapse of the left lower lobe was first observed in March 1936, and recurred in March 1937 with another exacerbation of bronchitis. In every instance complete re-expansion was observed, with clearing up of symptoms within four to ten weeks from the first attendance. In all four cases it was the left lower lobe that was affected; however, shortly before the period covered by the present series, a similar case affecting the right lower lobe was seen at the same clinic.

Lobar atelectasis following surgical operations and as a consequence of bronchial obstruction is now a well-recognized phenomenon. It has also been described as a complication of various pulmonary diseases, such as tuberculosis, bronchiectasis, pneumonia, and asthma; after injuries to the chest, after haemoptysis, and after the diagnostic injection of lipiodol into the bronchi (Bowen, 1929; Jacobaeus, Selander, and Westermarck, 1929; Jacobaeus and Westermarck, 1930; Clarke, 1930). It has been reported less frequently as a complication of a simple bronchitis (Jacobaeus and Westermarck, 1930; Maxwell, 1937); and in the reported cases has been accompanied by symptoms of acute illness. The four cases recorded above were of interest in that they presented symptoms no more acute than those commonly associated with an attack of bronchitis. An added importance is given to these cases by the recent discussions on the role of atelectasis of the lung in the pathogenesis of bronchiectasis (Findlay, 1935; Jennings, 1937; Lander and Davidson, 1938). As shown by Jennings, the bronchial dilatation which occurs in an atelectatic lobe is not necessarily permanent. Our observations, suggesting that the association of transient lobar atelectasis with catarrhal affections of the respiratory tract producing no specially acute symptoms is more frequent than is commonly realized, lend point to his plea that bronchial dilatation in an atelectatic lobe should not be pronounced to be a permanent condition until an adequate period of treatment has failed to effect re-expansion of the affected lobe.

Group III. Transient circumscribed consolidation. The remaining 21 cases did not fall into either of the above groups. We consider the essential lesion in them to have been a transient consolidation of the lung, for reasons to be discussed below, and therefore feel justified in including them in a common group. The following is an analysis of the clinical and radiological features of this group.

Age and sex. The ages of the patients ranged from 6 to 62 years. Six were under, and 15 over, the age of 14 years. There was no selective sex incidence, 11 being males and 10 females.

Occupation. No occupational factor could be detected; only two of the patients were engaged in out-door occupations.

Previous health. Ten patients had no history of previous respiratory disease; five had suffered from recurrent winter bronchitis; three had had pneumonia, and three pleurisy.

Onset of symptoms. The onset was insidious in 14 cases; in two pain in the chest was a presenting symptom, and in one haemoptysis. In four cases the symptoms dated from an acute upper respiratory infection, described as 'sore throat' in two and 'influenza' in two. As the latter two cases occurred in February 1937, it is possible that the infection may have been a true virus influenza.

Symptoms. On the patients' first attendance at the Dispensary, symptoms had generally been present for one to three weeks. Cough was present in all cases; it was generally productive, being described as 'dry' in three

only. In three cases there was complaint of blood-stained sputum. Excessive lassitude was common; it was noted in 11 cases. Dyspnoea on exertion (nine cases) and loss of weight (eight cases) were also common complaints. Pain in the chest was noted in six, and labial herpes in one case. It will be observed that the symptomatology resembles that of active pulmonary tuberculosis in many respects.

Incapacity. There was often very little interference with the patients' activities. In eight cases the patient had not been kept away from his usual occupation, and in six more it was noted that he had not been confined to bed. In the remaining seven, the maximum period of confinement to bed was seven days. Total periods of up to five weeks away from work occurred, but were usually rather on medical advice than from any feeling of continued incapacity.

Physical signs. In eight cases no abnormal physical signs were detected on examination of the chest. In nine there were localized signs in areas corresponding to those of the radiological changes noted below; of these, five showed localized râles only, two impairment of percussion-note with weak breath-sounds, one impaired percussion-note with râles, and one a localized area of weak breath-sounds. In five cases there were bilateral basal catarrhal signs.

Upper respiratory tract. Routine examination included inspection of the fauces and pharynx, but no detailed examination of the nose and sinuses. Enlarged and infected tonsils were noted in two cases, post-nasal catarrh in three, and gross dental caries in two.

Radiological appearances. The opacities observed in the radiograms were generally of medium rather homogeneous density, though in some a tendency to a coarse mottled appearance was evident. They were of not quite regular rounded outline with edges fading off into normal lung tissue. They varied in diameter from about 6 to 7 cm., affecting a large part of a lobe, down to about 2 cm., these smaller ones being localized in the costo-phrenic angle. These characteristics are shown in Plate 5, Figs. 3 and 4; we have chosen as illustrations neither the largest nor the smallest, but typical examples of these opacities. The localization of the opacities was predominantly at the bases of the lungs; the distribution in the radiological zones in 19 of the cases was as follows:

| | <i>Right</i> | <i>Left</i> |
|-----------------------|--------------|-------------|
| Upper zone | 1 | 0 |
| Middle zone | 2 | 3 |
| Lower zone | 5 | 8 |

In the remaining two cases, opacities similar to those observed in the other cases were present at both bases. Plate 6, Fig. 5 is an example of this type. Analysing the lower zone shadows further, we find that in three cases they were localized to the costo-phrenic angle, in three to the cardio-phrenic angle, and in the remainder they lay above the dome of the diaphragm. A small group (three cases), of which Plate 6, Fig. 6, is an example, showed

shadows lying just above the diaphragm of greater density than the majority and showing more definite mottling at the periphery. With regard to the duration of the abnormal appearances, complete resolution was eventually verified in all cases. In four, further radiograms taken three weeks after the first attendance showed complete clearing. In the majority of the remainder, such clearing was confirmed within six to eight weeks. Radiograms had not been repeated earlier than this, so that these times are certainly in excess of the actual duration of the lesions.

Discussion

Transient radiographic opacities of the lung have been recorded in a variety of conditions, apart from the well-recognized types of acute pneumonia.

1. In association with catarrhal infections, 'grippe', 'influenza', &c., such shadows have frequently been observed, and have most frequently been attributed to a mild or abortive form of pneumonia. Most of the reports come from institutions where routine radiological examination has been made. Jeanneret and Famé (1931) observed a small epidemic of 'grippe' among the personnel of a sanatorium, and examined all cases radiologically; they described two cases of 'pseudo-lobar broncho-pneumonia', characterized clinically by a benign course, without the severe symptoms usually associated with pneumonia, and radiologically by opacities of limited extent in a lower lobe. Teschendorf (1933) made radiological studies during an epidemic of 'grippe', and reported four cases presenting transient radiographic shadows in the lung-fields without pneumonic symptoms. Bezançon, Jacquelin, Lehman, and Tribout (1933) reported 50 cases of lung involvement in an 'epidemic of seasonal infections'. Among the cases they described a type which they regarded as a transition-form between an affection of the bronchi only and a frank pneumonia; their two illustrative cases of this sort showed definite radiographic opacities of the type under discussion, without pneumonic symptoms. Gallagher (1934) made complete clinical and radiological studies of the pulmonary involvement in respiratory infections occurring in the years 1932-3 and 1933-4 in a school of 350 boys aged 12 to 20 years. He described 16 cases of 'broncho-pneumonia' of limited extent, without the usual physical signs of consolidation in most instances, and without the severe symptoms of an acute pneumococcal pneumonia. There was an associated upper respiratory tract infection in all but one, and the maximum incidence of the cases was in the months January to May, when such infections were prevalent (cf. seasonal incidence of cases in present series, below). The radiographic changes were very similar to those of group III. They cleared more rapidly, but this may have been due to enforced rest in bed and superior environmental factors. Sayé (1935) studied cases of 'grippe' in the months February to May 1932 and 1933; he described several varieties of pulmonary involvement, of which the first (benign forms), the fourth (ambulatory forms), and possibly the second (forms of more

prolonged evolution, simulating tuberculosis), seem to belong to this group. Bowen (1935) described under the title 'acute influenza pneumonitis' cases which he had found by routine radiological examination of patients suffering from 'influenza' in Hawaii. The shadows were described as involving part of a lobe, usually basal, but sometimes in the upper lobes, and consisting of a confluent mottled fan-shaped or rounded area. In 1933, out of 271 cases of 'influenza', 89 cases of 'pneumonitis' were reported. In these cases there were no general symptoms and no increased respiration rate, such as are usually associated with pneumonia. Allen (1936) applied the term 'acute pneumonitis' to 'a form of respiratory infection characterised by a benign course, few physical signs, and roentgenological evidence of a localised inflammatory process in the lung'. He reported 68 cases, discovered by radiology, among 2,081 cases of 'respiratory disease', which included also 53 cases of lobar pneumonia and 16 of broncho-pneumonia.

In all these reports the term 'grippe' or 'influenza' probably indicates nothing more than an epidemic catarrh; there is no evidence that true virus influenza was responsible for the epidemics or endemics. Bowen (1935) defines the disease he terms 'influenza' as a 'mild acute respiratory infection, which is more prevalent some years than others, and which is familiarly referred to as "flu"'. In an outbreak of proved virus influenza in which the lung changes were especially studied, no comparable lesions were observed (Scadding, 1937).

2. Cases of similar type occurring apart from epidemics or the routine examination of cases of endemic catarrhal infections have been recorded by numerous authors. The earliest cases recorded were quoted under some such term as 'atypical pneumonia' or 'symptom-poor pneumonia' as a differential diagnosis of the early exudative lesions of tuberculosis, to which Wessler (1923) and Assmann (1925) first drew attention, and which will be discussed further below. Cases having all the characteristics of those quoted above were mentioned in this way by Kellner (1931, 1932, 1933), Leitner (1932), Löffler (1932 *a*), and Ameuille and Lejard (1932). Kellner (1932) expressed the opinion that many cases diagnosed as 'grippe' were really suffering from a mild benign broncho-pneumonia. The difficulty of the immediate differential diagnosis was stressed by all these authors; Ameuille and Lejard did not commit themselves definitely as to the nature of the lesion in most of their cases.

Sayago (1934), Davidson (1935), and Kluit (1936) recorded cases of mild respiratory infections characterized by fleeting radiographic opacities which also seem to fall into this group. Gill (1936) described a group of similar cases in children, and later (1938) added some cases in adults, to which he applied the term 'acute simple pneumonitis'. His description reads: 'cough of recent origin, anorexia, and loss of weight. There may be blood-stained expectoration. . . . The temperature is normal or slightly raised, the respiration rate is normal, and tachycardia is present. . . . An X-ray examination reveals opacities. . . . Within a week or two the symptoms,

signs and radiographic changes completely disappear.' Beaumont (1937) and Moncrieff (1937) have also referred to this condition under the same title. Maxwell (1938 *a, b*) has also described cases of 'pneumonitis', which he defines as a localized infection of the lung without gross toxæmia. He stated that the temperature and pulse-rate might be raised, but the respiration-rate was only slightly or not at all raised; the diagnosis might depend upon radiographic signs, and the prognosis was good. Nicholas and Agassiz (1938), discussing the radiographic appearances of pneumonia, recognize both 'primary low-grade' and 'atypical' pneumonias. The group which they classify as 'primary low-grade pneumonias' in children, and the localized broncho-pneumonic or solitary focal variety of their 'atypical pneumonias' were distinguishable from each other only by slight differences in radiographic appearance and by age-incidence, and probably could both be included in the same category as group III of the present series.

3. A group of cases presenting a similar clinical and radiological picture, but occurring in asthmatic subjects, has been described. Söderling (1935) gave case reports of five cases of this sort in asthmatic children, in many of whom eosinophilia was noted. Miller, Piness, Feingold, and Freidman (1935) recorded 11 cases of apparent broncho-pneumonia unaccompanied by severe symptoms in asthmatic children. They termed the condition 'allergic broncho-pneumonia' and attributed it either to bronchial obstruction leading to atelectasis or to 'allergic pulmonary infiltration'. Fever was noted in all cases. As will be seen from the numerous reports reviewed above, a similar condition is common in catarrhal affections of the respiratory tract, and there seems to be no justification for postulating any special allergic factor and placing cases occurring in asthmatic subjects in a separate category.

4. Jeanneret and Famé (1933) reported some very transient radiological opacities observed in the course of routine examination in both normal subjects and patients with pulmonary tuberculosis, without any symptoms whatever. They attributed them tentatively to atelectasis without supervening infection. As mentioned above, the same authors had previously (1931) recognized the existence of mild and transient pneumonic conditions, and they reported these additional cases as representing yet another cause of 'ombres radiologiques fugaces'. Faravelli (1937) has reported an extraordinary case in which an extensive shadow in the left lung of a young man, whose only symptoms were anorexia, pains in the shoulders, and slight fever, was observed to clear completely within fifteen hours of its first being detected.

5. Löffler (1932 *b*), discussing the differential diagnosis between tuberculous and non-tuberculous pulmonary infiltrations, described an interesting group of cases in which rapidly developing opacities were observed in the lung parenchyma, disappearing within a few days, and often reappearing in another part of the lung or in the opposite lung. They were accompanied by a well-marked eosinophilia. He thought they might be of various aetiologies, some being of tuberculous origin and others non-tuberculous, and

attributed them to pneumonia-like reaction in an allergic individual. He applied to them the non-committal name 'Succedanschatten'. Hansson (1937) reported a case in an asthmatic subject which he regarded as falling into this group. Sayé (1935) recorded a case which conformed with Löffler's description of 'Succedanschatten', but in which he thought the first opacity observed was tuberculous in origin, and three subsequent ones due to non-specific pneumonic processes. Whether such cases represent a separate disease process or are merely due to a fortuitous succession of lesions belonging to the groups previously discussed remains doubtful.

6. The observation that the first manifestation of pulmonary tuberculosis radiologically is often a circumscribed area of homogeneous opacity, resembling in quality the opacities produced by pulmonary consolidations and usually observed in the infra-clavicular regions was first recorded by Wessler (1923) and Assmann (1925). This early exudative lesion of pulmonary tuberculosis, of which, by its very nature, there can be little opportunity for pathological study, has been studied extensively radiologically and clinically, and it was soon established that it might appear in parts of the lung fields other than the infra-clavicular regions, and occasionally might heal, leaving little trace of its presence, within a few months (Redeker, 1926; Klingenstein, 1926; Assmann, 1927; Fishberg, 1928; Löffler, 1932*a*; Wingfield, 1937; and others). Similar lesions are observed appearing in previously unaffected areas of the lung-fields in the course of established pulmonary tuberculosis. They are invariably a manifestation of re-infection; whether this is endogenous or exogenous is still a matter of controversy. They appear in the literature under various names—'re-infection focus', 'Assmann focus', 'Frühinfiltrat' in the German literature, and 'secondary lesion' in Wingfield's nomenclature. These lesions are a possible cause of transient radiographic opacities of the lungs, and reference has already been made to the extensive literature on their differentiation from non-tuberculous lesions producing similar shadows.

Another type of lung lesion associated with tuberculosis, which may give rise to opacities in the radiogram which slowly disappear, is that first described by Eliasberg and Neuland (1920) in children as 'epituberculosis'. The nature of the cases described under this title has recently been discussed by Goldberg and Gasul (1930) and by Reichle (1933). They hardly come within the scope of the present discussion; their resolution extends over several months at least and generally some residual abnormality is left in the lung tissue in the region of the opacity, even if it is only the old primary complex around which the 'epituberculous' infiltration occurred.

The nature of the lesion in group III. The cases of group III conform well with the description of those discussed in the first three sections of the preceding survey of the literature. They presented none of the special features by which cases of sections 4 and 5 were distinguished. The only other possibility to be considered is that some of the cases may have been early exudative tuberculous foci of the type discussed in section 6. Consider-

ing the cases as a group, the uniformly rapid and complete clearing of the lesions, their predominantly basal localization, the presence of catarrhal symptoms, and the failure in every case to demonstrate tubercle bacilli in the sputum or to discover any collateral evidence of tuberculosis, is sufficient to exclude this possibility. Proved cases of early tuberculous infiltrations, though they are observed occasionally to clear completely, leaving a normal radiographic appearance, always follow a more prolonged course; we have been unable to find a record of a case in which an infiltration, proved to be tuberculous by being the only lung lesion in a patient whose sputum contained tubercle bacilli, regressed completely in less than six months.

There is no important difference between the published descriptions of the cases of benign pulmonary involvement in epidemic catarrhal conditions (section 1), those of the sporadic cases of similar type (section 2), those reported in the course of asthmatic conditions (section 3), and those of group III of the present series. Those cases which have been observed as the result of routine radiography in acute respiratory catarrhal conditions seem, on the whole, to have shown resolution earlier than those which appeared sporadically in out-patient practice; but this difference is obviously explicable by the selective effect of the conditions under which the two groups were observed. In all, catarrhal conditions of the respiratory tract were complicated by lung involvement causing transient, localized radiographic opacities without symptoms suggestive of pneumonia of the classical types. There is some evidence that cases of group III were more frequently observed at times of the year when catarrhal affections are common (see below, 'seasonal incidence'). It seems probable, therefore, that the opacities represent localized inflammatory consolidations of the lung occurring in the course of catarrhal infections of the respiratory tract. The shadows observed were not related to the linear pulmonary striations, and seemed to bear no anatomical relation to any one part of the normal lung pattern. Their generally rounded shape and the absence of evidence of mediastinal shift in the case of the larger ones is evidence against their being due solely to lobular atelectasis. The quality of the shadow is similar to that found in known conditions of pulmonary consolidation; it has been noted above that the shadows cast by unresolved acute pneumonia were indistinguishable from the more extensive examples of group III.

Opportunities for pathological study of lesions following so benign a course must of necessity be very rare. Only one of the authors whose studies have been mentioned in sections 1 to 3, above, claims to have made pathological observations. Bowen (1935) describes the appearances in two lungs 'showing small areas of pneumonitis. These areas were firm to palpation, not nodular. On section they were moist with serous and haemorrhagic exudate. . . . Histologic examination showed some cellular infiltration of the smallest bronchioles and of the alveolar walls. Many alveoli were filled with red cells, others with serum. Some alveoli had considerable numbers of mononuclear and epithelial cells, but polynuclear cells were not numerous. In

other words, sections showed an early exudative inflammatory process.' Unfortunately, no clinical records of these cases are given, and it is not made clear on what grounds the author assumed that they belonged to the same group as his clinical series. It can be stated, therefore, that at present no direct pathological observations are available. Clinical considerations may help, however, in understanding the probable nature of the lesion; but before discussing these, it seems advisable to discuss briefly some general aspects of nomenclature.

A note on the nomenclature of pulmonary inflammations. 'L'art de raisonner consiste surtout dans une langue bien faite' (Laennec, 1826).

In its broadest sense the term 'pneumonia', like its synonym 'pneumonitis', could be applied to any inflammation of the lung parenchyma; but a universal convention has confined its application to those forms of inflammation which are characterized predominantly by exudation into the pulmonary alveoli. This definition excludes the fibrotic stages of pulmonary tuberculosis and those forms of suppurative pulmonary inflammation characterized by gross cavitation and abscess formation. After these have been excluded, there remains a miscellaneous variety of conditions which may legitimately be included under the heading 'pneumonia'. The nomenclature of these has been based sometimes on morbid anatomy, sometimes on clinical aetiology, and sometimes on bacteriology. This becomes evident when such terms as lobar pneumonia, hypostatic pneumonia, and tuberculous pneumonia are considered. To make a complete diagnosis, both aetiological and anatomical terms must be included in the description of a pneumonia; for example, whereas 'lobar pneumonia' by itself might indicate one of several widely differing conditions, 'pneumococcus type I right lower lobar pneumonia' is a specific diagnosis.

In the nomenclature of the acute pneumonias much confusion has arisen, mainly on account of the tendency to attempt to correlate the anatomical distribution of the lesion with its pathogenesis. It seems possible to recognize two fundamentally distinct mechanisms of production of acute pneumonias.

1. The first is the process established by the classical work of Blake and Cecil (1920). They showed that in pneumonia produced in monkeys by the intra-tracheal injection of cultures of pneumococci or haemolytic streptococci, the organisms invaded the lung tissue by penetration of the bronchial walls, and then spread by the perivascular, peribronchial, and septal interstitial tissue and lymphatics, reaching the alveoli from the interstitial tissues. The initial lesion in all cases was an interstitial inflammation. Whether the lesion was lobar or lobular seemed to depend mainly upon the resistance shown by the interstitial tissues to the particular organism, and also upon the dose used. This process is analogous with cellulitis in other tissues; its most characteristic occurrence in man is in the primary pneumococcal pneumonias. It will be termed acute specific pneumonia. The term 'specific' is defensible on the ground that this reaction occurs as the result of a pure infection of the lung parenchyma with an organism belonging to one of a few well-defined groups.

Mention must be made of several authors who have described experimental pneumococcal pneumonias in which the method of propagation of the inflammatory process through the lung tissue appeared to be different from that described by Blake and Cecil. In every instance in which an important deviation from their description has been observed, there was a complicating factor, absent from their experiments. Thus Permar (1923) described experimental pneumonia arising as an acute inflammatory reaction of the trachea, bronchial tree, alveolar ducts, atria, and alveoli, causing lobular foci of consolidation which later coalesced; but he used rabbits, which were anaesthetized with ether, and a volume of injected culture (1 c.c.) considerably greater in relation to the size of the animal than that used by Blake and Cecil. Terrell, Robertson, and Coggeshall (1933) using dogs, and Gunn and Nungester (1936) using rats, described an initial peripheral focus from which the lesion spread by extension through the lung parenchyma and by the flow of oedema fluid along the smaller air passages. In both these investigations, the infecting pneumococci were injected into the periphery of the lung, suspended in a tenacious medium—starch being used by Terrell, Robertson, and Coggeshall, and mucin by Gunn and Nungester. In addition, the former authors used very heavy morphine medication. Under the conditions of these experiments, it would clearly be impossible for the resulting lesion to show the same initial character as was observed by Blake and Cecil. However initiated, an important feature of pneumococcal and other pneumonias of this type is that they behave as acute specific infections. The role of hypersensitivity of the infected individual, the importance of which has been stressed by Lauche (1928) and supported by the experiments of Sharpe and Blake (1930), Lindau (1933), and Fried (1933), cannot be discussed here; it can be noted that in these experiments pneumonia was produced as a specific response to endotracheal injection of substances to which the animal had been rendered hypersensitive.

2. The other mode of production of acute pneumonia is by aspiration of infected material down the air passages into the alveoli. Obvious examples of this type are the pneumonias associated with aspiration of food, in laryngeal palsies, and following anaesthetics. Small bronchi or bronchioles become blocked with infective material, which is then drawn down to the alveoli by absorption of the air beyond the block; when the condition is fully developed, with alveolar exudate, there may be no sign of persisting atelectasis. The initial lesions in the experimental pneumococcal pneumonias of Terrell, Robertson, and Coggeshall (1933), and Gunn and Nungester (1936) were probably of this type. The latter authors described lesions produced by the injection of mucin alone; in some of the rats so injected they observed pneumonic reactions of varying extent, but usually poor in fibrin, which might persist as long as three days. Kline and Meltzer (1915) also described, in dogs which had received intrabronchial injections of various unorganized substances, 'lesions which macroscopically could not be distinguished from those produced by insufflation of pneumococci'. The importance of

aspiration of infected mucus as a cause of pneumonia has been emphasized by Amberson (1937) who showed that lipiodol introduced into the nose of a sleeping individual could be demonstrated in the alveoli, an observation which had previously been made by Quinn and Meyer (1929). The possibility of oily substances introduced into the pharynx descending to the alveoli and there giving rise to inflammatory reactions is shown by numerous recent reports of oil-aspiration pneumonia (Ikeda, 1937). Since these various foreign substances have been shown to behave in this manner, there can be no doubt that excessive mucous secretion can by the same mechanism produce pneumonic reactions in the course of catarrhal infections of the respiratory tract, and that in these cases, the production of the pneumonic reaction does not depend primarily upon the nature of the bacterial flora. To the large group of pneumonias which depend upon this mechanism for their initiation, the term 'aspiration pneumonia' will be applied. The term 'broncho-pneumonia' is avoided because it has acquired so many confusing associations that its use in this sense could only add to the confusion; and the term 'bronchogenic pneumonia' proposed by Burrell (1938) has the disadvantage that acute specific pneumonia is, in a strict sense, primarily bronchogenic.

These two distinct mechanisms can give rise to lesions whose gross anatomy is similar. In some circumstances, especially in children, an acute specific pneumonia can be anatomically lobular. On the other hand, an aspiration pneumonia can be lobar in form, either by confluence of lobular aspiration foci, or as a complication of a massive lobar collapse. It is well recognized also that an acute specific pneumonia, or cellulitis of the lung, can arise, and probably frequently does arise, as a complication of a descending catarrhal inflammation of the bronchi.

The pathogenesis of the pulmonary lesion in group III. Of the alternative origins of the pulmonary consolidation in group III, aspiration is the more probable. The points in favour of this hypothesis are firstly, that this form of consolidation arises in the course of catarrhal conditions of the respiratory tract; secondly, that where such observations have been recorded, the organisms known to produce acute specific pneumonias have been found seldom or not at all in cases of this type. Complete bacteriological studies were not possible in the cases of this series; but in five cases which clearly belonged to the same group, seen at Hammersmith Hospital by one of us (J. G. S.), examination of the sputum in the more acute stages failed to reveal pneumococci; *Str. viridans* and *N. pharyngis* being the organisms most commonly found. Gallagher (1934), in his 16 cases among schoolboys, found *H. influenzae* in four, *Str. viridans* in five, and staphylococcus in one. Bowen (1935) found in his cases of 'acute influenza pneumonitis' that sputum culture generally showed *Str. viridans*, almost never pneumococci or Pfeiffer's bacillus. Allen (1936) in 'acute pneumonitis' found that 'in a few group IV pneumococci were isolated, in others no pneumococci were found'. This view is in agreement with that of Beaumont, quoted by Gill (1938), that

the 'syndrome could be produced by partial obstruction of one or more bronchioles by a muco-purulent inflammatory exudate'. Maxwell (1938 *b*), on the other hand, seems to regard the condition as a mild or abortive pneumonia of the acute specific type, its benign course being determined by a 'good local and general resistance'. Abortive acute pneumococcal lobar pneumonia is not rare, and presents a clinical picture which in most instances is distinguishable by its more definite onset and termination; but it is possible that a small area of pneumonia of the acute specific type occurring in the course of a catarrhal infection may occasionally give rise to the picture of the group under discussion.

The nomenclature of group III. Whichever view is correct, it is clear that the term 'pneumonia' can properly be applied to the cases of this group. As specific causative organisms cannot be identified, and probably are not involved, it has seemed reasonable to complete the title with terms indicative of anatomical distribution as shown radiologically, and of the clinical course—a method used in previous papers by one of us on some other not yet widely recognized varieties of pneumonia (Scadding 1936, 1937 *b*, 1938). We therefore propose the name 'benign circumscribed pneumonia'. It is hoped that terms thus elaborated are clearly descriptive, without implying unverified hypotheses. Should further investigation establish a specific aetiology for these conditions, or any sub-group of them, a term descriptive of this factor can be added to the name already adopted.

The word 'pneumonitis', which has been applied to this condition, is simply a synonym of 'pneumonia' and means nothing more than 'inflammation of the lung'. The use of it without qualification to denote one of the many types of pulmonary inflammation involves a convention that may not be universally recognized, and will inevitably lead to much confusion. As Burrell (1938) remarks, 'All these cases should be grouped as pneumonia and it seems unnecessary to introduce the word pneumonitis unless all cases are called pneumonitis and the word pneumonia dropped.'

Incidence of transient radiographic shadows. After due allowance has been made for the special character of the clinic at which these cases were observed, some idea of the relative frequency of the conditions described may be obtained from the fact that during the same period a total of 1,220 new cases were examined. The 29 cases which form the subject of this paper were thus 2.4 per cent. of the total, while the 21 cases of benign circumscribed pneumonia formed 1.7 per cent. of all new cases seen. These figures show that such cases occur with sufficient frequency in the practice of a clinic mainly devoted to chest disease to render knowledge of their characteristics a matter of some importance; there can be no doubt that in a community where mild respiratory infection is a commonplace their incidence is considerable.

Seasonal incidence. On examining the incidence of the cases month by month, the following observations can be made; that of the 21 cases of group III in two years, 13 were seen in the months of February, March, and

April; that the last three months of the year together produced no case of group III in two years; and that in groups I and II the only notable difference in the monthly incidence was a similar paucity of cases in the last months of the year, only one occurring in the months September to December.

Differential diagnosis. The differentiation between the various groups into which the cases have been divided has already been indicated. In relation to other pulmonary diseases, the following points may be considered.

Group I. Unresolved acute pneumonia. The differential diagnosis of these cases from other pulmonary diseases is similar to that of group III, from which the history alone was often the only distinguishing characteristic.

Group II. Transient lobar atelectasis. In addition to the differentiation of these cases of transient lobar atelectasis from permanent atelectasis with bronchiectasis, which has already been mentioned, they may also need to be distinguished from atelectasis due to bronchial obstruction by foreign body or by new growth. The course of the disease will usually solve this problem, but it will often be advisable to make a decision before waiting for re-expansion. Atelectasis due to new growth occasionally re-expands temporarily, owing to necrosis of the stenosing part of the growth, and spontaneous re-expansion of an atelectatic lobe does not therefore entirely exclude the possibility of malignant disease. In all cases of doubt, bronchoscopy should be performed and will nearly always lead to a definite diagnosis.

Group III. Benign circumscribed pneumonia. As noted above, it was the difficulty of distinguishing this condition from early exudative *pulmonary tuberculosis* that led to most of the earlier references to it in the literature. While, considering the group as a whole, there was no difficulty in eliminating the tubercle bacillus as the aetiological agent, in many individual cases it could be eliminated only by serial radiological examinations. The radiogram is never sufficiently characteristic to justify a dogmatic diagnosis of pulmonary tuberculosis without supporting evidence and without a period of observation. An important point is the presence of catarrhal symptoms; a history of such symptoms, with production of muco-purulent sputum in which tubercle bacilli cannot be found, in a patient presenting a localized radiographic opacity in the lung, is strong evidence that the opacity is not due to tuberculosis. An early tuberculous lesion producing a shadow of this type, without cavitation, would be unlikely to give rise to well-marked catarrhal symptoms.

The possibility that *chronic inflammatory lesions*, such as bronchiectasis and areas of pulmonary fibrosis, may underlie an apparent benign circumscribed pneumonia often arises. The occurrence of acute pneumonic reactions around such chronic lesions is well recognized; they have been called 'épipneumopathies' by Benda and Mollard (1936) and 'secondary pneumonitis' by Gill (1938). In cases in which the history is suggestive, the presence of chronic lesions can be excluded only by appropriate investigation after an interval to allow for clearing of the more acute lesions.

New growths of lung will be confused only with the more extensive benign

pneumonias. There should be no confusion with the typical atelectatic picture produced by a growth in a main bronchus, and the more peripheral growths are usually much more radio-opaque than localized consolidations.

Abscesses of the lung and chronic suppurative pneumonias. It has recently been suggested by one of us (Scadding, 1938) that many cases that are conventionally described as abscesses of the lung of unknown aetiology should be regarded rather as chronic suppurative pneumonias. We have been able to observe the earliest stages of several such cases; and in them the symptomatology and radiological appearances were at first very similar to those of benign circumscribed pneumonia. It seems therefore that in the more extensive and severe examples of the latter there may be a possibility of the condition lapsing into a chronic suppurative phase, and even proceeding to gross abscess formation. The suggestion is made tentatively that the condition we have described as benign circumscribed pneumonia may sometimes be the early stage of a chronic suppurative pneumonia. If the former condition be regarded as a localized aspiration pneumonia, it is easy to conceive of some difference in the bacterial flora of the mucous plug in the bronchus of the affected area being the deciding factor in the production of a suppurative lesion. Maxwell (1938 *b*) also suggests that there may be a relation between the benign pulmonary consolidations, his 'pneumonitis', and primary lung abscesses; he considers that it is a poor local resistance of the lung tissue to infection that may determine the formation of a lung abscess. It is interesting that Laennec (1826) thought that abscesses of the lung might arise from 'péripneumonies partielles'. Such problems cannot be solved finally without more complete knowledge of the pathogenesis of both conditions than is at present available. It is certain that in the large majority of cases in which an initial diagnosis of benign circumscribed pneumonia can be made, the condition proceeds uneventfully to complete resolution.

Summary.

1. An analysis is presented of 29 cases, seen at a tuberculosis clinic during the course of two years, in which mild respiratory catarrhal symptoms were associated with transient opacities in the lung radiogram.
2. When those in which the opacities could be attributed to delayed resolution of acute pneumonia and to pulmonary atelectasis were excluded, there remained 21 cases in which the pulmonary lesion was regarded as a small area of consolidation arising without specially acute symptoms and following a benign course to complete resolution.
3. The literature relating to such lesions is reviewed and their pathogenesis discussed.
4. It is concluded that the localized consolidations probably represent aspiration pneumonias arising in the course of catarrhal infections of the respiratory tract, and are of frequent occurrence.

5. The nomenclature of pulmonary inflammations is discussed. The term 'pneumonitis', which has been applied to these lesions, is criticized, and 'benign circumscribed pneumonia' is suggested as a more precise description.

6. The differential diagnosis of the various groups of transient radiological opacities mentioned is briefly discussed.

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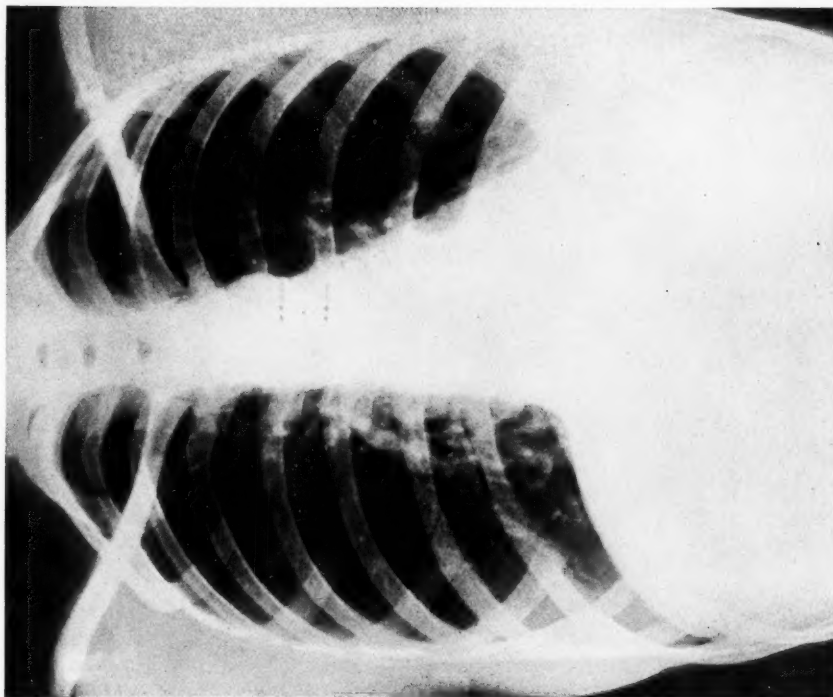


FIG. 1. Female, aged 20 years, machinist. Previous history irrelevant. For four weeks cough followed by slight pain at the left base. Off work for one week. Physical signs—dullness at left base, with numerous coarse râles, and a small area of faint tubular breath-sounds. Radiogram shows collapse of the left lower lobe, with some shadowing above the line of the collapse

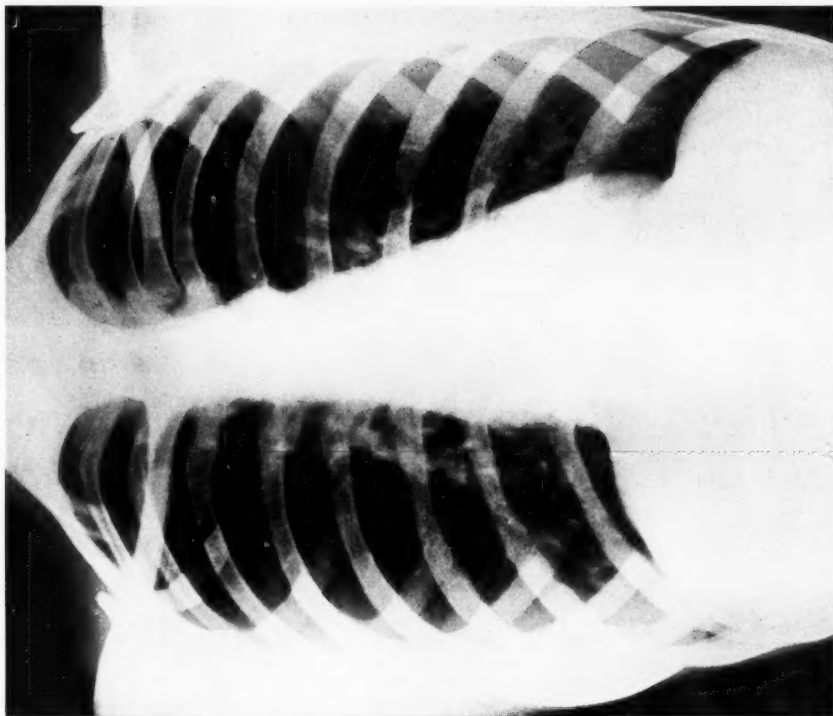


FIG. 2. The same case. Radiogram four weeks later, showing re-expansion of affected lobe and clearing of abnormal opacities



FIG. 3. Male, labourer, aged 25 years. Subject to winter coughs for several years. Recent slight loss of weight, lassitude, dyspnoea on exertion, and slight haemoptysis. Not confined to bed. Physical signs indefinite. Radiogram shows diffuse mottled opacity in left middle zone. A radiogram three weeks later showed complete clearing of the opacity

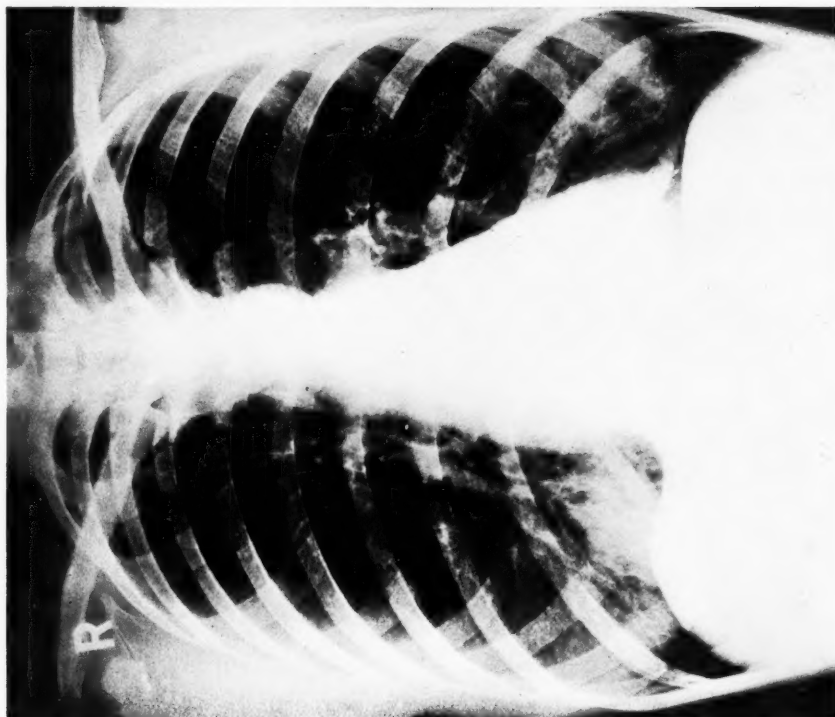


FIG. 4. Housewife, aged 38 years. Previous history irrelevant. For three weeks, cough, sputum, lassitude, dyspnoea on exertion, and hoarseness of voice. Not confined to bed. Physical signs—weak breath-sounds at right base. Radiogram shows localized well-defined opacity at right base. A further radiogram after six weeks showed complete resolution

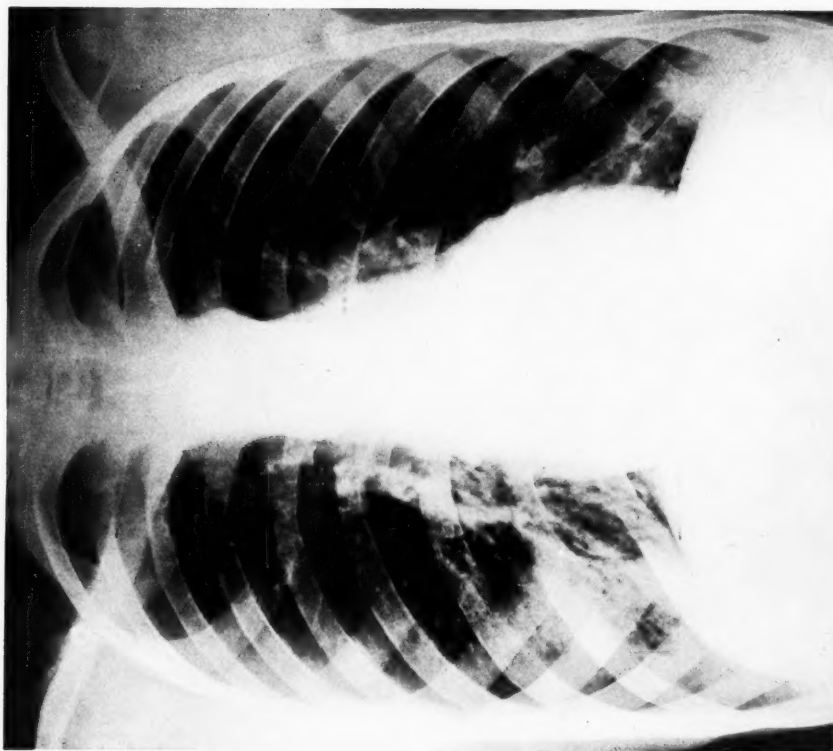


FIG. 5. Male, aged 20 years, messenger. Previous history irrelevant. For five weeks, cough, sputum, loss of weight, lassitude, slight pain in the left side of chest. Off work, but not confined to bed. Physical signs indefinite. Radiogram shows well-defined opacities at both bases, more extensive at the right. Further radiograms showed considerable clearing in three weeks, and complete clearing in seven weeks

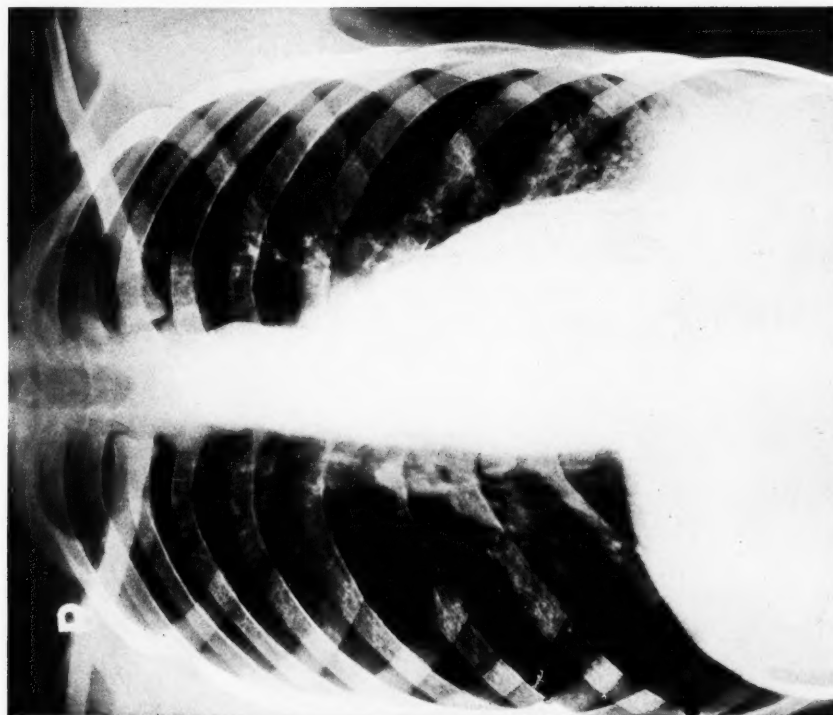
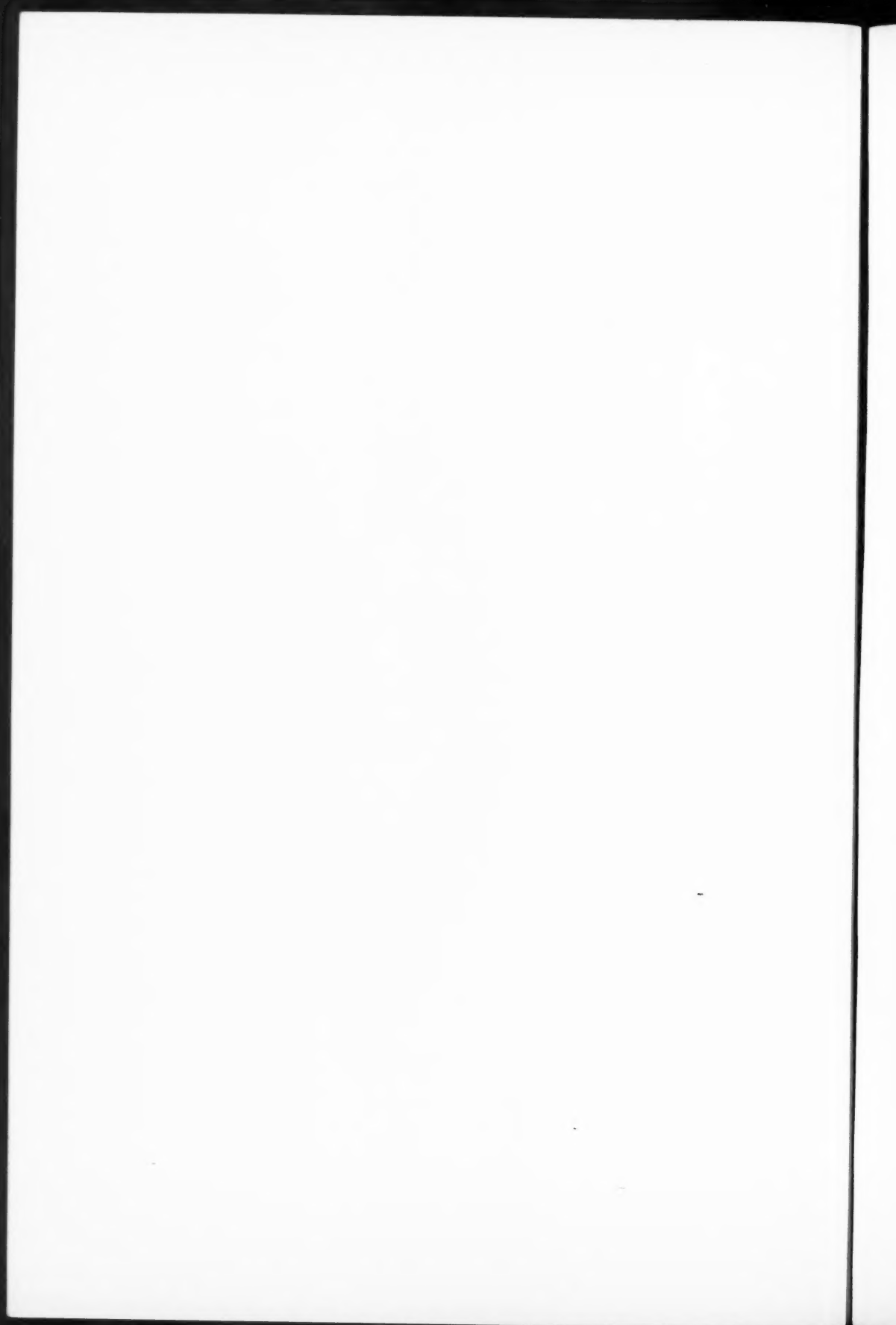


FIG. 6. Male, aged 19 years, unemployed. Previous history irrelevant. Insidious onset, over three months, of cough, sputum, lassitude, loss of weight, dyspnoea, and pain in the left side of chest. Not confined to bed. Physical signs—râles at left base. Radiogram shows dense opacity above left diaphragm with mottled upper margin. Further radiogram after six weeks showed complete resolution



HEREDITARY ECTODERMAL DYSPLASIA OF ANHYDROTIC TYPE¹

By P. C. C. DE SILVA

With Plates 7 to 9

THIS condition is only one of a number of hereditary ectodermal defects. It is separated from the others for two reasons:

1. It is the only one showing absence of sweat glands.
2. It shows sex-linked inheritance and is incompletely recessive (Levit, 1936).

Case Reports

Case 1. The patient is a male Singhalese aged 37 years, and the only child of unrelated parents. His maternal uncle is said to be like him and to have the same symptoms, including deficient dentition, hypotrichosis, and anhydrosis, but to be quite normal in height and build. The patient complains of epistaxis, occurring once every month since birth up to the present time, lasting one day.

He has an old man's face, with thin, shiny, atrophic, and wrinkled skin (Plate 7, Fig. 3). Its colour is very dark, almost black, and darker than the average Singhalese. The cheeks and the medial parts of the forehead are lighter complexioned, with enlarged hair follicles. He is undersized for his race and age; height 5 ft. 3 in., with chest measurement 29 in., and weight 94 lb., as against the standard weight of 131 lb. He has prominent supra-orbital ridges and very large mastoid processes. He has a very high forehead and some prominent veins on the forehead and scalp. His ears are small and rounded, with normal lobes. His lips are thick and prominent, the upper more so than the lower. The bridge of the nose is depressed, though not flat, but the tip is quite pointed and narrow. The nostrils are wide, but the nose is not saddle-shaped. The hair on the scalp and face is patchy in distribution. He has only six teeth, all of the permanent dentition, and all in the upper jaw; he states that he has never had any others and does not remember having lost any permanent teeth. The teeth are the upper four incisors and the upper two canines. The medial incisors are broad, short, and widely-spaced. The canines are also short, but have the normal pointed shape. X-rays show no unerupted teeth buds. The alveolar margin is pointed and narrow. The nails are normal in shape and colour, but excessively hard and dry. He says it is impossible to cut either his finger or toe nails unless they have been soaked in cold water for two or three minutes.

The tongue is very long, and he can rest its tip on the tip of his nose. He can also bend his head downwards and touch his sternum opposite the

¹ Received November 9, 1938.

second rib with the tip of his tongue. The palate and throat appear normal, but he complains of dysphagia. He takes very small mouthfuls of solids, and even these are swallowed only with the help of water. Till the age of 15 years the only solids he had were rusks soaked in milk. Before this age, on attempting to eat any other solids, vomiting occurred. His pharynx is narrow, but the pharyngeal mucous membrane is normal. As already described, the skin on the face is very thin and atrophic, but quite elastic all over the body. No subcutaneous fat is visible anywhere on the body. His healing powers after injury are very poor. No signs of epithelial regeneration were seen three weeks after skin section, cut with aseptic precautions, without sutures, and in the absence of sepsis.

There is not a vestige of hair anywhere on his body, except for a few scanty hairs in both axillae. No hair follicles can be seen under a magnifying lens, except on the scalp, axillae, and face. He has never sweated in his life. Sections of skin taken from the dorsal aspect of the left forearm and the anterior aspect of the right thigh show no sweat glands, no sebaceous glands, and no hair follicles. He always feels a severe burning sensation all over his body during the day and sometimes at night. He has about five cold baths a day, or if he cannot get his usual baths, he wets his undershirt and wears it. Epistaxis comes on about once a month and is associated with fever (malaria). The hands are small, and there is a double curve on each little finger. Both nipples are present. Corneal opacities are seen at four o'clock on the very edge of the right cornea. Lachrymation is excessive. Slit lamp examination showed that the 'corneal opacities are of congenital origin. No blood-vessels extend to opacities. The appearances are against syphilis.' The fundi were normal.

The joints show excessive mobility. He can do contortionist tricks, such as placing one foot round the back of his neck and hopping on the other. Slight nasal obstruction was present on the left side, with septal deviation to the left, and dry crusts, the appearances being those of atrophic rhinitis. The blood-pressure varied between 90/70 and 100/70. The temperature ranged from 96.2° F. at 8 a.m. to 99.4° at 5 p.m., and the pulse from 56 at 1 p.m. to 80 at 8 a.m. After standing in the sun for half an hour, the temperature rose from 98° to 99.4° F. The respiration rate was 40.

There was hypertrophy of the external genitalia (Plate 7, Fig. 4). Testicular sensation was normal. The patient is quite definite that puberty was delayed up to somewhere between 18 and 20 years. He married in his 28th year. A normal male child was born two years later, and died of convulsions, aged 20 days. He left school at 16 years, being then in Standard 6. The speech was normal; he can speak moderately good English, good Singhalese and Tamil. He impresses one as having no control over his speech. He rambles gaily, though quite rationally, from one topic to another. He is happy-go-lucky in temperament and very cheerful in spite of extreme difficulties, hardships, disappointments, and unemployment in his life. He has no independence nor initiative; is very obedient and willing to be examined. He feels quite strong and has excessive libido. Periodic bitemporal and frontal headaches have occurred three times a month from the age of 14 years. These are present only on very hot and sunny days, and from 11 a.m. to 1.30 p.m. He never feels hungry, can be without a meal for two days, and usually has one meal a day. Thirst is marked and he takes 16 glasses of water and other liquids a day. The blood Wassermann reaction is negative. X-rays of skull show a small sella turcica, a very large frontal sinus, exostoses and thickening of the inner plate of the cranium,

and marked obtuseness of the mandibular angle (Plate 7, Fig. 5). (For family pedigree see Fig. 1.)

Case 2. C. D. The patient is a boy aged 12½ years, the second of three brothers. His elder brother is normal, his younger brother died in infancy. A maternal uncle, aged 19 years, was born with a good head of hair, but has been bald since childhood, has no eyebrows, and very scanty eyelashes.

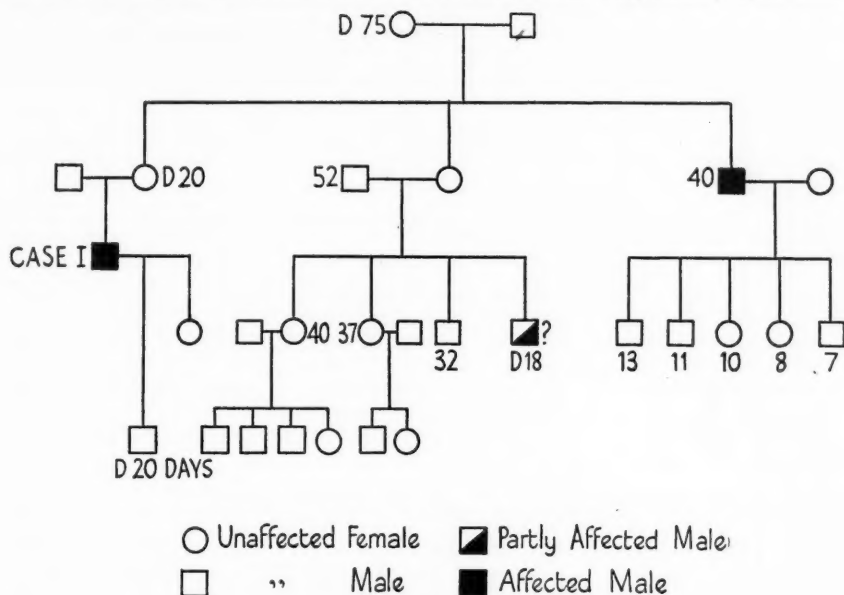


FIG. 1. Pedigree of Case 1.

The uncle's beard and moustache are very scanty, and he has no axillary, pubic, limb, or body hair. He sweats profusely, and heat intolerance is marked. There is follicular hyperkeratosis on the trunk. The facies is normal with prominent supra-orbital ridges. His mentality is normal. There are a few papules on the face. He is fair complexioned (*café au lait*), the nails are rudimentary, narrow, and the nail margin concave. He alleges that he lost all his nails four years ago and grew them again. The thumb nails and some toe nails have longitudinal furrows. The teeth are all present and in good condition.

At the age of 3, the patient had a violent temper. If he was refused anything he wanted he used to bang his head on the floor, and this used to give rise to slight epistaxis every second or third day. He had a purulent discharge from the nose with a maggot infestation at four years of age. Since the purulent discharge has ceased, he has had no epistaxis. Examination shows that the patient has an old man's face, with thin, shiny, atrophic skin, soft like an infant's. His complexion is darker than the average Singhalese. He is undersized for his race and age. Height 4 ft. 1 in. Weight 50 lb. (as against the standard weight of 55 lb.). The supra-orbital ridges are not prominent. The eyes are set widely apart (intercanthal width 1.15 in.). The face looks squashed from above downwards, due to his having a very small chin (0.8 in. from lower lip to top of chin).

and a very high forehead. He has prominent veins on the scalp and forehead. His ears are large and rounded. His eyes are clear and lustrous, and the sclerotics normal. The bridge of his nose is flattened and the tip pointed (Plate 8, Figs. 6 and 7). The alae nasi are wide, and the nose is saddle-shaped but otherwise normal. The lips are thick, the upper thicker than the lower. He has no eyebrows, but the eyelashes are normal.

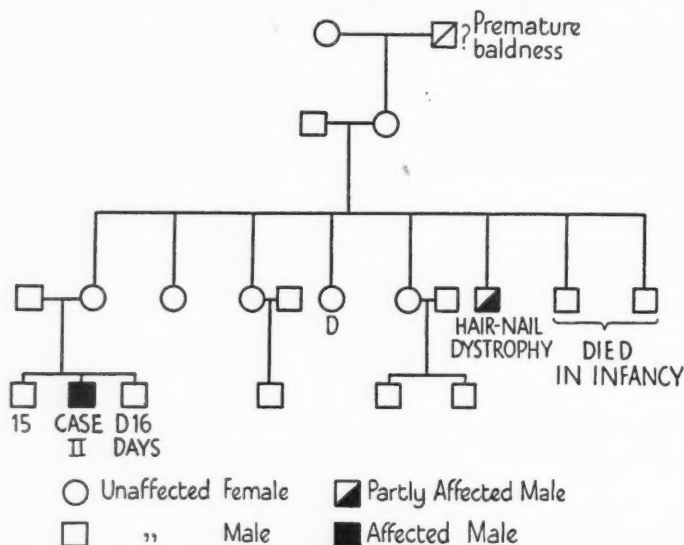


FIG. 2. Pedigree of Case 2

The hair on the scalp is thin, long, brittle, lack-lustre, lanugo-like, and scanty. No hair is present on the body.

He was born with two canine-like incisor teeth in upper jaw. The permanent teeth appeared at five years. He has two upper lateral incisors, long, pointed, and peg-shaped, and two canines which are shorter than the incisors. In the lower jaw are two canines only. All are permanent teeth. X-rays show one unerupted right lower incisor tooth (Plate 8, Fig. 8). In the hands the little fingers are curved, the palms small. The other fingers are normal in length and shape. The tongue is very long; he can rest the tip of his tongue on the sternum (as in Case 1), but he cannot rest it on the tip of his nose. He cannot take solid foods, as they make him choke. The skin contains no hair follicles, and he cannot sweat. There is extreme heat intolerance, and he takes over twenty baths daily. Thirst is excessive. Temperature 99.8° F., and pulse 90, at 9.30 a.m. The left nipple is completely absent; the right is represented by a pigmented macule. No mammary glands can be palpated. His mental condition is normal, but he cannot attend school owing to extreme heat intolerance. He is very sensitive and timid, short-tempered, and vicious. The central nervous system, the eyes, and the cornea appear normal.

He has not attained puberty yet. He will not allow examination of the sex organs, but his father alleges they are of normal size. X-rays show that the sella turcica is of normal size, but more widely opened than usual. (For family pedigree see Fig. 2.)

Case 3. The patient is an adult male Singhalese, of unknown age, a travelling bread-seller by occupation. He is married and has four children, who are said to be normal. One child, who did not talk or take solids, died of dropsy at seven years. The patient's parents are both dead, and their relationship is unknown. He has had epistaxis, sometimes preceded by headache, from the time he can remember, every three to twelve months. Blood comes from the nose drop by drop for about five minutes.

On examination the patient is well built, broader and taller than the average Singhalese. Height 5 ft. 7 in. Weight 122 lb. (Standard weight 150 lb.) He has a dark brown complexion, but is much lighter in complexion than Cases 1 and 2. Hyperpigmentation (black) is present round the eyes, in a butterfly wing fashion across the nose, and on the lower part of the forehead. The hair on the head is long and thin, and tied in a knot at the back, the long hair being over 30 in. in length. The scalp is visible through the hair, and the hair edge is high, but only about half an inch above the ears. The eyebrows are rudimentary, only the inner half inch being present. The beard and moustache are normal in distribution, but sparse, and he shaves only once a week. Hair is present on the body only in the axillae. The forehead is high, and he has prominent supra-orbital ridges and high cheek bones. The nose has a depressed bridge, a pointed tip, and wide nostrils, but there is no nasal obstruction. The skin is shiny, thin, and atrophic; xeroderma is present on both legs. In the upper jaw the following teeth are present: 2 peg-shaped incisors, 2 left molars, 1 right premolar, 2 left premolars, 1 right molar; and in the lower jaw: right and left canines, 1 right premolar, 1 left premolar, 1 right molar, 1 left molar. He has lost 1 upper incisor and 2 lower incisors. He has thus a total of 14 teeth remaining, and has lost 3 teeth, making 17 teeth in all. The tongue is long, but not as long as in Cases 1 and 2.

His occupation of a bread-seller keeps him on the road during the hottest part of the day, but he has never sweated. He is, however, protected from the direct rays of the sun by the large bread basket, about 3 ft. high with a circumference of about 3 ft., which he carries on his head. He bathes once a day. He complains of a burning sensation during the hot part of the day and on hot, stuffy nights. His temperature varies between 99° and 100° F., and the pulse between 70 and 80. The hands are normal, but the finger ends bulbous. The little fingers do not show a double curve, as in the other cases. The eyes appear normal. The testes are normal, but there is penile hypertrophy. Hunger and thirst are normal. In the nervous system the knee jerks are present only on reinforcement, and hyperalgesia to pinprick is generalized, but the findings were otherwise normal. He has never attended school, is quite illiterate, and does not know his age (not extraordinary in Ceylon for a man of his class). He is rather dull and apathetic, and answers questions hesitatingly. The mentality is definitely, though slightly, below the average. X-rays show that the sella turcica is small and very widely opened, and that there is a large frontal sinus (Plate 8, Fig. 9).

Case 4. The patient is an Indian Tamil, aged 45 years, unmarried, and a pavement cigar-seller. He does not remember any members of his family who resemble him; both parents are dead, and were not related. Eight years ago he had epistaxis for two to three days. On examination he is well built but short. Height 4 ft. 11½ in. Weight 88 lb. (standard weight is 134 lb.). He is much broader than Cases 1 and 2. The complexion is dark, his expression cheerful, and the face round, with very prominent supra-orbital

ridges. The nose has a flattened bridge and pointed tip, with slightly widened nostrils, and is saddle-shaped. The forehead is broad and the hair edge high. Prominent veins are visible in the temporal region. The mouth is wide. The lips are not as prominent or as full as in the other cases, and the upper is thicker than the lower. The ears are small. The eyes are deep-set and very small. Hyperpigmentation is present below the eyes and on the lower part of the forehead. The height of the forehead is 2.5 in., and the lower lip to chin measurement is 1 in., with a squashed appearance from above downwards. The width between the eyes is narrow, being 1 in. (Plate 9, Fig. 10). The eyelashes are present, but there are no eyebrows. The skin on the legs and thighs is scaly, shiny, and atrophic, but thin and soft elsewhere. The distribution of hair on the head and face is the same as in Case 1.

Teeth are present in the upper jaw: 1 right molar and 1 left molar (Plate 9, Fig. 11). The lower jaw is edentulous, as he lost 5 or 6 lower jaw teeth two years ago. The skin of the scalp is shiny and thin. The mastoid processes are normal. The tongue is not as long as in Cases 1 and 2. He has never sweated. He bathes only two or three times a week; he complains of 'burning', especially on back, worse on hot days, and he wears his shirt soaked with water during the day. Heat intolerance is excessive; he cannot stand the glare and heat of the day, and so wears dark glasses or sits in the shade. Even when he was examined he wetted his shirt and stood by a desk fan to cool himself. The hands are very small, and both little fingers have double curves. The nails are normal. The eyes are normal. The central nervous system is normal except for generalized hyperalgesia to pinprick. Puberty developed after the eighteenth year, and his genital development is normal, but he has no sexual desire. Temperature 99° F., and pulse, at 12 noon, 80. Hunger is normal. He never went to school, and is quite illiterate, but much more intelligent than Case 3. He carries on an independent business as a cigar-seller on a pavement in Colombo, but takes the precaution of sitting in the shade. He is quite shrewd and mentally wide awake. He answers questions promptly and to the point. His intelligence is above the normal for a man of his class and education. X-rays show a small sella turcica, but opened wider than normal.

Review of Literature

The first cases were recorded in India by Wedderburn in 1838, who reported 10 male cases in a Hindu family in Sind. Darwin quoted a letter from Wedderburn which clearly proves that these cases belong to the anhydrotic type. Thadani in 1921 reported a family also in Sind with this syndrome. The first cases in the white races were reported in 1848 by Thurnam, who showed two cases before the Medical and Chirurgical Society of London, and also referred to two Jewish brothers reported by Danz in 1792. Though Danz promised a fuller report, this was never published. The total number of cases reported (excluding the Indian cases) is 48. We have excluded Wedderburn's cases because no full details are available and we are not sure of the total number of cases reported by Thadani. If these cases are added, the total exceeds 60. Smith in 1929 collected a total of 15 cases from the literature and added one of her own, but we find that she

has omitted a number of cases which undoubtedly belong to this group, namely, the cases of Harwood (1903), von Moos (1919), Cockayne (1920), Apfelfthaler (1925), Oliver and Gilbert (1926), Schaer (1927), Harris (1928), Janitzkaja and Rjabow (1928). Since Smith's paper was published, 19 more cases have been reported up to 1936.

The racial distribution is interesting. Cases have been reported in England (18), America (9), S. Africa (1, of English descent), Germany (7, including one of German descent in U.S.A.), Russia (2), Sindhis in India (about 10), in Jews (3), Sweden (1), Switzerland (4), and Holland (2, including one of Dutch descent in America). No cases have been reported in the Negro or Mongolian races. The Latin races, too, as far as I am aware, have not produced any case.²

Age distribution. Cases have been reported at all ages from infancy to the sixth decade. The oldest case was aged 58 years (Thurnam, 1848). The condition has apparently no influence on the longevity of the patient.

Sex distribution. Out of the total of 47 cases we find 39 males and eight females. If Wedderburn's 10 males and our four males are added, the figures read 51 males to eight females. The eight females were reported by Williams (1848), Goeckermann (1920), Walter and Schaer (1927) two cases, Cove-Smith (1930) two cases, Ass (1929), and Gordon and Jamieson (1931). We have deliberately omitted Weech's (1929) female case, as we do not think she belongs to the anhydrotic group. There is clearly a preponderance of males, but the females, eight, definitely prove that this is not a strictly sex-linked recessive. Cockayne (1933) and Rushton (1934) have classified these cases according to the mode of inheritance: (1) Sex-linked recessive; (2) Dominant.

Levit (1936) thinks, however, that the condition is always determined by a sex-linked gene, which is not always completely recessive. The two groups are clinically indistinguishable. We have, therefore, not separated them. In the family groups, of which the pedigrees are illustrated in Cockayne's book (1933), and in those published more recently by Fleischmann (1931), Bowen (1932), Hill (1933), Clarke and McCance (1934), Rushton (1934), Schwarz (1935), Battersby (1936), and Thannhauser (1936), transmission occurs either through unaffected or affected females, and there is no well authenticated case of a male transmitting the defect to his son or his son's son. Levit's (1936) view, therefore, is probably correct. The affected females usually have some deficiency of teeth, and their hair may be scanty, but they are seldom unable to sweat. The two sisters recorded by Walter and Schaer (1927), however, had never sweated and had complete absence of teeth. There are also a few examples of males with the syndrome incomplete. In two of our cases we have been able to find ectodermal defects in antecedents, and their pedigrees are shown. Case 1 in our series has a maternal uncle with all the cardinal signs, and a maternal uncle of

² Brain (1937) has shown two cases, a brother and sister, before the Section for the Study of Disease in Children, Royal Society of Medicine, in October 1937.

Case 2 has a hair and nail dystrophy. Case 3 knows nothing of his family, and Case 4 says he is the only affected member of his family. Cases 1 and 3 are married, but all their children are stated to be normal.

Ectodermal defects without anhydrosis are much commoner than with it, and various combinations are seen. Weber (1929) in an excellent article details these conditions.

Symptomatology

Skin. In all the cases the skin is described as thin, dry, glossy, pliable, transparent, with prominent veins, and sometimes wrinkled. In two of our cases there was hyperpigmentation of a slight degree. All four of our cases had exactly the same appearance, and we have described this as thin, dry, soft, wrinkled and atrophic looking.

Histological examination of the skin has been made by several authors, and in one of our cases skin sections were taken from the dorsal aspect of the forearm and from the anterior aspect of the thigh. These were kindly examined for us by Professor Karunaratne of the Ceylon Medical College. His report says:—'Epidermis. There is a general thinning of the epidermis with marked cornification. Rete pegs are imperfectly formed and present only in a few places. Pigment present in the basal layers, but normal for a dark-skinned individual.'

Dermis and subcutaneous tissue. The papillae are rudimentary, only a few well-formed ones seen. Vascularity is normal, but no sweat glands, hair follicles or sebaceous glands are seen. Elastic tissue is present though diminished in amount and fragmented.

Sweat. Every male reported, except four, had complete and permanent anhydrosis (Falconer, 1929; Battersby, 1936; Thannhauser, 1936). None of our cases ever sweated, and their skins were absolutely dry when we examined them. It is curious to note that in Rademaker's (1932) case, though microscopic section of skin showed sweat glands and was reported as normal, yet the patient never sweated, and even after an injection of 1 mg. of pilocarpine no sweat secretion was perceptible.

All authors speak of the extreme heat intolerance (Guilford, 1883; Smith, 1929; Schwarz, 1935). Case 1 in our series has five to six baths a day and wetted his shirt in the intervals. Case 2 has ten to twenty baths a day and goes about bare-bodied most of the time. His parents tell us that he jumps into any running stream or the sea as often as he can manage. Even at night he runs out and has a bath. In Case 3 the heat intolerance is not marked, though there is no sweating. Case 4 wets his shirt frequently and wears it till dry, and then re-wets it. The same procedure is followed by the uncle of Case 1, who works in a Government office. Patients in Ceylon are considerably handicapped by the absence of winter. It is only at night and during a rainy day that they get a partial respite from their suffering.

This, however, does not seem to have interfered with the length of their lives—the oldest is 45 years.

In a normal person the heat lost by evaporation from the skin is 14.5 per cent.; by radiation and conduction from the skin 73 per cent.; the balance is lost by the urine and lungs (Howell, 1912).³ Sensible perspiration is a true secretion by the sweat glands and is absent in these patients, but there is no difference in the insensible perspiration between them and normal persons (Wechselmann and Loewy, 1911). 'The belief that the principal function of perspiration (sensible and insensible) is to regulate or help to regulate the heat of the body is considerably strengthened by a study of these patients. The patients are healthy and live to normal age, and the sole, inadequate, physiological function is the failure to radiate sufficient heat when subjected to a hot atmosphere or to vigorous exercise' (McKee and Andrews, 1924).

Skin eruptions. Cases 3 and 4 showed mild xeroderma of the legs. Cases 1 and 4 showed papular lesions of the face. These were few in number, inconspicuous and situated near the nose. They had the appearance of degenerated sebaceous glands. Papular lesions on the face have been described by various authors (Wechselmann and Loewy, 1911; Christ, 1913; Strandberg, 1918; Goeckermann, 1920; McKee and Andrews, 1924; Falconer, 1929; Hill, 1933). These lesions were diagnosed by different authors as milium, xeroderma, adenoma sebaceum, and degenerated sebaceous glands with hyperkeratosis.

Teeth. Abnormal dentition is present in every case and, in fact, is one of the three basic signs of this condition, the other two being anhydrosis and hypotrichosis. The abnormality varies from complete anodontia (Harwood, 1904; Wechselmann and Loewy, 1911; Gibbs, 1915; von Moos, 1919; Apfelfthaler, 1925; Walter and Schaer, 1927; Kerley, 1930; Nager, 1933; and Battersby, 1936), to the absence of a few teeth. The abnormality extends to both the deciduous and permanent dentitions. In our patients, Cases 1 and 2 had six teeth each, all incisors or canines, Case 1 had all in the maxilla, Case 2, four in the maxilla and two in the mandible. Case 3 had nineteen teeth and Case 4 had twelve teeth. The earlier writers all stressed the fact that the lower jaw never held any teeth. This is proved to be wrong, not only by our series, but also by Oliver and Gilbert (1926), Smith (1929), Weech (1929), Gordon and Jamieson (1931), Rademaker (1933), Hiebert and Garland (1934), and Schwarz (1935), Case 2. All authors are also agreed that the teeth that are present are abnormal in size, shape, and colour. They are invariably described as peg-shaped or 'gimlet-like' (McKee and Andrews, 1924), with a broad base and pointed tip. Often they are twisted round so that they face laterally, and a portion of the posterior surface can be viewed from the front; this description refers to the incisors and canines only. The molars are usually normal in shape. The teeth are smaller than normal and of a muddy, yellow colour. Except

³ Wright (1934) gives the heat lost by evaporation from the skin as 25 per cent.

for Case 1, whose teeth are square, short, and uneven, all our other cases showed these characteristics. In addition the alveolar margin, where no teeth are present, is usually very narrow and resembles a knife board. This was present in all our cases.

Hair. The character of the hair on the scalp has been uniformly described as dry, fine, lanugo-like, and sparse, with the scalp showing through it. In our cases we noticed that the hair may be pulled out with ease, without pain and without breaking it. We also noticed that the hair is longer and more abundant along the vertex, but more especially over the occipital region. The hair margin, both laterally and posteriorly, ended much higher than in a normal person. The hair on the limbs is completely absent. The hair on the face has been noted as present by most authors. Two of our adult cases (1 and 4) had the same characteristic patchy distribution and neither shaved more than once a week. The hair distribution on the face has been detailed in the history of Case 1. Eyebrows are usually totally absent. In Cases 1 and 2 eyebrows were completely absent, but in Cases 3 and 4 of this series the inner third or less was present. Eyelashes are usually reported as scanty, normal, or absent. They were present in all our cases, though scanty in Case 1, especially on the lower lids. Axillary hair is present, though scanty in all three of our adult cases. Most of the authors, except Tendlau (1902), report that the axillary hair is either absent or scanty. Pubic hair was completely absent in all our cases. Many of the cases reported had scanty pubic hair, but Guilford reported it as normal in a male aged 48 years (Tendlau, 1902; McKee and Andrews, 1924). Lanugo hair on the body has been completely absent in all our cases, though it has been reported as present, though sparse, in a few cases (Wechselmann and Loewy, 1911; Falconer, 1929; Gordon and Jamieson, 1931).

Nails. Dysplasia of the nails is frequent (Blaisdell and Cunningham, 1917; Strandberg, 1918; Goeckermann, 1920; McKee and Andrews, 1924; Weech, 1929; Gordon and Jamieson, 1931; Whitwell, 1931; Hill, 1933; Clarke and McCance, 1934; and Schwarz, 1935). Case 1 in our series showed nails normal in shape and colour but unduly hard. In Case 2 the nails were normal. His uncle, who showed a dystrophy of hair and nails, had small, rudimentary nails with longitudinal furrows, lost all his nails at the age of 15 years and grew them again. Case 3 had bulbous ends to his fingers, i.e. 'club-shaped', but his nails were normal. Case 4 showed markedly convex nails with longitudinal furrows on the nails of the index fingers. The hardness of the nails as seen in Case 1 has been noted by a few previous writers, and we believe it is due to the excessive cornification which was clearly seen in the microscopic sections of his skin.

Mammary glands. Absent mammary glands have been reported by Ascher (1898), Tendlau (1902), Ass (1929), Falconer (1929), and Clarke and McCance (1934). Smith's first case showed no gland tissue, though nipples were present. Case 2 in our series showed no mammae, and only a rudi-

mentary, pigmented macule replaced the right nipple. All our other cases had normal breasts and nipples.

Lachrymal glands. Thurnam's (1848) two cases showed no lachrymal secretion. Rushton's (1934) case is reported as 'never having had tears till a few months ago, and still had extremely few' (aged $4\frac{1}{2}$ years). Case 4 in our series told us that he never had any tears, but all our other cases were normal. Three other cases show absence of lachrymation (Thurnam, 1848, two cases; Rushton, 1934). The lachrymal buds are of ectodermal origin and form at the third month of intra-uterine life, i.e. at the same time as the teeth are laid down, and it is strange that absence or diminution of tears has not been noticed in more patients.

Face. The face is very characteristic in this disease. As we have stated already, it was the facial resemblance to Case 2 that helped us to collect the other cases. In spite of the great racial differences between all the cases in the white races and our own, yet the resemblance is striking. The forehead is high and wide; the supra-orbital ridges are invariably prominent; the bridge of the nose is depressed and resembles a congenital syphilitic nose. It was this feature that confused many early observers, and some of their cases were treated for syphilis. Pseudo-rhagades, or fine linear wrinkles radiating from the naso-labial folds or near the eyelids, have been noted by McKee and Andrews (1924), Falconer (1929), and Hill (1933). They were present in Cases 1, 2, and 4 in this series. The nose has invariably been described as saddle-shaped, and in our series only Case 1 did not show this appearance. The cause of the depressed bridge, Smith (1929) thinks, is the same as in syphilis, namely, an osteo-perichondritis. The depression of the nasal bridge is accentuated by the prominent supra-orbital ridges. The palpebral fissures are narrow, and Case 4 had quite definite enophthalmos. The lips are uniformly described as thick, everted, and protruding. All our cases answered to this description, except Case 4 in which the lips were normal. Where this sign is specially mentioned, the only other case with normal lips is Schwarz's (1935) Case 2. The thick, muscular lips are due to the absence of teeth. The chin is very small and pointed. The whole effect is of a face squashed from above downwards, the upper half being much longer than the lower. Clarke and McCance (1934) aptly described it as a 'nutcracker' face. The angle of the jaw is obtuse. This can clearly be seen in the X-rays of Case 1.

Nose. Most of the cases showed atrophic rhinitis with the history of a chronic discharge, crusting, or sometimes ozaena. Our Case 4 had a very wide left nasal cavity with a marked deviation and angulation of the nasal septum to the right. Cases 1, 2, and 4 showed chronic rhinitis. Case 4 was seen by an oto-rhinologist who thought that the septal deviation, which was gross, was not traumatic in origin but probably congenital or developmental. The chronic atrophic rhinitis in this case was, he thought, due to the septal deviation. All our cases gave a history of epistaxis, and, except in Case 4, this was recurrent and periodic. We do not think this is due to

rhinitis because of its peculiar periodicity and its copious amount. Epistaxis has also been reported by Gordon and Jamieson (1931), Smith (1929), and Rushton (1934). In all these cases the epistaxis was recurrent but, as in our cases, it ceased after a time. This has been so striking a symptom in all our cases that it is difficult for us to ignore its importance. The sense of smell has been reported as absent by two authors. Our cases (1 and 4) had complete absence of the sense of smell.

Tongue. A feature in this series was the long tongue. Case 1 could place the tip of his tongue on the tip of his nose, and by bending his head downwards and forwards, the tongue could be made to touch the sternum. Case 2 could do the latter, but not the former. Case 3 had a tongue longer than normal, but could do neither of these tricks. Case 4 had a normal tongue. The only previous writer to mention this sign is Rademaker (1933), who reported a very large tongue in his patient aged 2 years. The tongue is one of the few mesodermal structures which are affected in this condition.

Dysphagia. All our cases, except Case 3, complained of dysphagia. We find this symptom recorded only by Clarke and McCance (1934). The dysphagia was mainly for solid foods. Case 1 took practically no solids till the age of 15 years, as he used to choke when he tried to swallow. Case 2 still cannot take solids. On examination we find that the pharynx is narrow, but the mucous membrane normal. Cockayne, in a personal communication, thinks that the dysphagia is due to a dry mucous membrane, and the fact that Case 1 complains of scanty saliva is in favour of this explanation.

Ears. In Case 4 we noticed that the ears were small and rounded, and normal in position, with adherent lobes. In the other cases they were normal. Many authors (Ascher, 1898; Wechselsmann and Loewy, 1911; Hill, 1933; Battersby, 1936; Nager, 1920; McKee and Andrews, 1924) report deformed ears.

Eyes. Case 1 showed corneal opacities at the edge of the cornea. An ophthalmologist, after a slit-lamp examination, said these were congenital.

Voice. Voice changes, usually hoarseness, are reported by several writers. In our cases the only alteration noticed, which was not striking, was a high pitched effeminate voice. As the mucous membrane from the nose downwards is dry and atrophic, one expects the larynx too to be affected, and the voice to be abnormal.

Nervous system. Though the nervous system is ectodermal in origin, very few abnormalities have been reported, and certainly no gross malformations. Thurnam (1848) has reported the post-mortem appearances of the brain. The only other case that came to an autopsy was Zeligs' in 1932, but unfortunately the report was very meagre and unsatisfactory; apparently no examination of the brain or pituitary gland was made. No organic changes in the central nervous system have been reported. Case 1 could not discriminate between the point and the head of a pin. In Case 3 hyperalgesia

to pinprick was generalized; he could discriminate between the point and the head of a pin. Case 4 also showed hyperalgesia to pinprick. No other changes from normal were ascertainable in the central nervous system. The hyperalgesia may be due to the fact that in the absence of hair follicles the end organs of sensory nerve fibres are more numerous on the skin than in the normal person.

Mentality. Tendlau (1902), Wechselmann and Loewy (1911), Christ (1913), Strandberg (1918), and Nager (1920), report mental deficiency. All the other cases are reported as normal. Cases 1 and 3 are below the average, though not to a marked extent. Cases 2 and 4 are, if anything, above normal. Case 1 shows interesting character traits—lack of shyness, garrulity, and parasitism. All the other cases show excessive timidity and sensitivity. Case 2 did not allow us to examine him if his parents were not with him. The uncle of Case 1, we understand, is also very timid and sensitive about his condition. He absolutely refused to be examined by us. They are all conscious of the fact, and extremely so, that they are not as other men. They are usually good natured, but once they are roused they are very short tempered and vicious, but soon revert to their usual calm.

Palms and soles. Most authors report the palms and soles as thick, slightly scaly, and cracked. In our cases we noticed that there were extra creases on the palms and fingers. The palms of Case 1 were very rough. As all our patients walk barefoot, examination of the soles was not of value.

Little finger. There is a curious double curve on the little fingers of both hands in Cases 1, 2, and 4. This resembles closely the curve one often sees in Mongolism. We have endeavoured to show this in the photograph of Case 4. This has not been described before in the literature, and the explanation is obscure. In this group this is the third mesodermal structure to be affected. As three out of our four cases showed it, it can hardly be a coincidence. Case 3, which did not show the above dystrophy, showed, however, bulbous ends to all his fingers.

Genitals. Falconer (1929) reports under-development of the genitals. Case 1 showed over-development of testes and penis (Plate 7, Fig. 4). Case 3 showed over-development of the penis only.

Osseous system. Though mesodermal in origin, the osseous system shows certain characteristic changes. The prominent supra-orbital ridges have been noted by every writer except Smith (1929), who records it as absent. Cases 1 and 3 showed large frontal sinuses. Case 3 had very high cheekbones which projected laterally. Cases 1 and 4 had very large mastoid processes. Cases 1, 2, and 4 showed thickening of the inner plate of the skull as compared with normal (Thannhauser, 1936; Weech, 1929). The sella turcica is small, but in Cases 2, 3, 4 it is more widely opened than is normal. This has been remarked upon by a few previous writers. Thannhauser (1936) found a low fasting blood-sugar and a flat sugar-tolerance curve. Case 1 showed a normal fasting blood-sugar and a normal

sugar-tolerance curve (Smith, 1929; Gordon and Jamieson, 1931; Hiebert and Garland, 1934).

Pigmentation. As far as we are aware, no mention is made of this by any of the authors except Thannhauser (1936), who found scattered pigmentation on the trunk and abdomen. In this series we can only say that Cases 1 and 2 were much darker than the average Singhalese.

Basal metabolic rate. The basal metabolic rate has been investigated by a few writers, and the findings vary from minus 20 per cent. to plus 59 per cent. In Case 1 in our series it was plus 27 per cent.

Blood calcium and phosphorus when done have been found to be normal except in Smith's (1929) case, where the blood calcium recorded is 15.5 mg. per cent. In Case 1 in this series the blood calcium was 11.5 mg. per cent.

The blood Wassermann reaction has been done in 18 cases and without exception has been reported as negative. We were able to do this in Case 1 only, and here, too, it was negative.

Differential Diagnosis

The differential diagnosis of this condition is not difficult. These cases have been confused with congenital syphilis, progeria, and endocrine dyscrasias. It is the face with the saddle-shaped nose which is likely to be mistaken for that of congenital syphilis, but if more careful and closer observation is undertaken, one is at once struck by the peculiar hypotrichosis and the character of the hair, which is never met with in syphilis. The absence of eyebrows is striking, and is at once noticeable to the most casual of observers. If one opens the mouth and looks at the teeth in an adult case, then opinion is doubly assured, for here not only is there often a marked deficiency in the number of teeth, especially of the molars and premolars, but there is a gross malformation of whatever teeth are present, and this malformation is strikingly different from the Hutchinsonian teeth of congenital syphilis. While the latter have broad, concave tips, the former are peg-shaped, with a broad base and pointed tip, often discoloured and twisted round on their axes. The pseudo-rhagades described in this group are situated round the nose, and are much finer than in syphilis where they are more common round the mouth. Anhydrosis is characteristic and, if confirmed by an examination of serial sections of the skin, is pathognomonic of this condition. The absence of hair on the body, especially on the pubes in adults, is striking.

Progeria, as described in Gilford's (1897) original paper, has some points of resemblance with this condition, small stature with poor musculature, a somewhat similar facies, hypotrichosis of the head and body, scanty eyebrows, absence or diminution of subcutaneous fat, chronic rhinitis, prominent veins on the extremities, absent mammary glands with unusually small or absent nipples, thin, soft, pliable, and dry skin, quiet and gentle disposition, poor appetite (cf. Cases 1 and 4 of the present series), and a high voice. In progeria, however, the lips are thin, the tongue short and small, sweating

is normal and even excessive at times, and the dwarfism is marked, no case being over three feet in height. The head is very large in proportion to the small body, the epiphyses of the long bones, especially those at the lower end of the humeri and femora, are very large, the supra-orbital ridges are not prominent, the superficial and deep reflexes are absent, a systolic murmur is present at the apex, and the arteries are thick, tortuous, and atheromatous. The temperature, instead of being frequently above normal, is always normal or subnormal. A notable lack of energy and extreme fatigue are also present. Gilford states that none of the three primary tissues, ectoderm, mesoderm, and endoderm, is affected more than the others, and considers that progeria is acquired and not congenital. Many of the resemblances between the anhydrotic ectodermal dysplasia and progeria are due to the premature senility, which is the chief feature of the latter, and are not present at birth. Falconer (1929), nevertheless, holds that progeria is identical with the major ectodermal defect, and it is evident that the two conditions can be confused, for Hutchinson's (1886) case, which was Case 2 in Gilford's original paper, has been included by Smith (1929) and Schwarz (1935) in their list of cases of anhydrotic ectodermal dysplasia. Harris (1928), too, presented his case as one of progeria before the Royal Society of Medicine. In the subsequent discussion, both Cockayne and Parkes Weber agreed that it was a case of the major ectodermal defect, and this was proved later by a biopsy of the skin, which showed the usual absence of sweat and sebaceous glands.

The anterior lobe of the pituitary gland is derived from ectoderm, and the symptoms due to its decreased function, which resemble those present in this condition are: (1) late maturity (Cases 1 and 4), (2) thin smooth skin, (3) scanty growth of hair of axilla, pubes, and beard, and absence of hair on the trunk and limbs; in children the skin is smooth and elastic, while in adults it is dry, wrinkled, and atrophic, (4) diminished secretion of sweat, and (5) small sella turcica. On the other hand, the prominent supra-orbital ridges, large frontal sinuses, large mastoid processes, exostoses and thickening of the inner plate of the skull, and the large tongue are evidence that the function of the anterior lobe of the pituitary gland is adequate. The pituitary gland appears to exert its effects on the body by bringing to structural and functional fulfilment the thyroid, the parathyroids, the adrenals, and the gonads. With deficiency of the anterior lobe there is failure to acquire secondary sexual characters (cf. lack of pubic hair and high pitched voices in our cases) and stunting of growth. The age of onset of puberty has unfortunately not been recorded by any of the writers. In Cases 1 and 4 it was quite definite that puberty was delayed till the age of 18 years, Case 3 could not remember, and Case 2, aged 13 years, has not yet reached puberty, though the average for Ceylon is between 12 and 13 years of age. Case 4 has never had any sexual libido, though he gets normal erections and the size of his external genitalia is normal. The high effeminate voice found in our cases and also in that of McKee and Andrews (1924) is

also slight evidence in favour of a gonadal deficiency in males. On the other hand, Case 1 had excessive libido with hypertrophy of penis and testes, and Case 3 had penile hypertrophy.

Aetiology

Individual signs and symptoms resemble those produced by endocrine disorders, but some of them, such as the absence of tooth germs, are present at birth, and cannot be due to endocrine deficiency. Others are not so clearly congenital, but until we obtain post-mortem or other evidence of structural or functional changes, the case for the endocrine origin must remain not proven. Falconer's (1929) view that the ectodermal dysplasia is a *forme fruste* of progeria is untenable. We are left with the conclusion that this is a hereditary condition due to a gene mutation in the X-chromosome, and that it is sex-linked, but not completely recessive. Its inheritance is therefore analogous to that of red-green blindness.

Prognosis

Thurnam's (1848) two cases, the oldest in the literature, were aged 58 and 59 years. Our oldest case was aged 45 years. The general opinion among all writers is that there is no shortening of life. The only disability is the excessive heat intolerance. As for treatment, many gland preparations have been tried in several of these cases without any success.

Summary

1. Four cases of hereditary ectodermal dysplasia of anhydrotic type are reported from Ceylon—three in Singhalese and one in a Tamil—all males.
2. A review of the literature is given. A total of 48 cases has been collected (excluding all Indian cases and the present series).
3. The symptomatology is reviewed. The present series demonstrates the following symptoms which have not been noted as commonly occurring in previous cases: epistaxis, no lachrymation in one case, long tongue, double curve of little fingers, clubbing of fingers in one case, large frontal sinuses, large mastoid processes, dysphagia and congenital corneal opacities in one case.
4. The differential diagnosis between this group and congenital syphilis, progeria, and other endocrine dyscrasias is discussed.
5. The condition is primarily due to a gene mutation in the X-chromosome. It is sex-linked but not completely recessive. The female transmitter, if she shows the defect at all usually shows it in a modified form.

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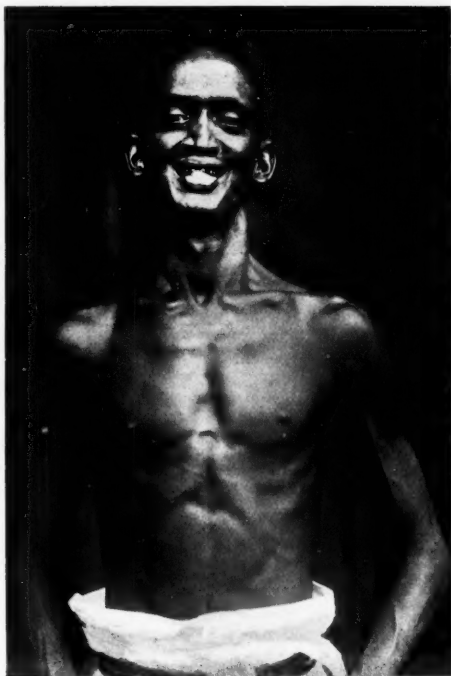


FIG. 3. CASE 1. Note the scanty hair, large tongue, prominent supra-orbital ridges, prominent superficial veins, thick lips, deficient dentition, and absent eyebrows



FIG. 4. CASE 1. Note the external genital hypertrophy, and broad upper lip



FIG. 5. CASE 1. X-ray of skull. Note the small sella turcica, large frontal sinus, acellular mastoid processes, and very obtuse mandibular angle



FIG. 6

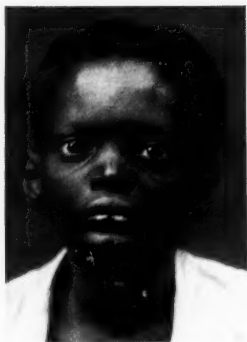


FIG. 7



FIG. 8

FIG. 6. CASE 2. Note the scanty hair, absent eyebrows, saddle-shaped nose, thick lips, small chin, and prominent superficial veins. FIG. 7. CASE 2. Note the scanty hair, wide forehead, saddle-shaped nose, thick lips, and wide inter-orbital space. FIG. 8. CASE 2. Shows the peculiar peg-shaped teeth. The six teeth seen in the photograph are all the erupted teeth that the patient possessed



FIG. 9. CASE 3. X-ray of skull. Note the small sella turcica, more widely opened than usual, and the large frontal sinus



FIG. 10. CASE 4. Note the scanty hair, patchy distribution of the beard, prominent supra-orbital ridges, saddle-shaped nose, prominent scalp veins, and absent eyebrows

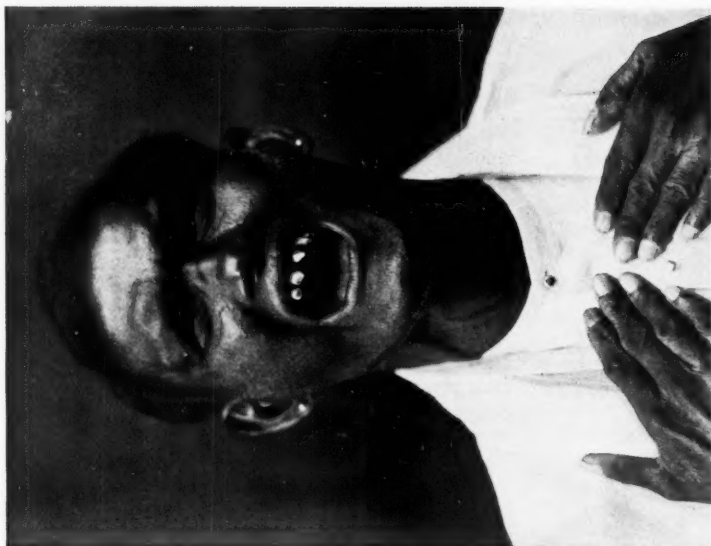


FIG. 11. CASE 4. Shows the peculiar peg-shaped teeth, and the double curve of the little fingers

THE SECRETIN TEST OF PANCREATIC FUNCTION¹

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Introduction

THOUGH it was in 1902 that Bayliss and Starling discovered the secretin effect, it was not until 1933 that secretin was isolated. In that year Professor Hammarsten of the Department of Biochemistry of the Caroline Institute in Stockholm succeeded in obtaining a crystalline salt of secretin. Among his collaborators Ågren should particularly be mentioned. Ågren and Hammarsten succeeded in 1937 in the delicate task of splitting secretin enzymatically without its activity being lost. On the basis of their experience with the purification of secretin Hammarsten and Ågren devised a method for the manufacture of commercial secretin.² From the pharmacological point of view this secretin closely resembles the crystalline product, and is free from the undesirable effects which made the use of earlier preparations inadvisable. Further, it is free from cholecystokinin, the hormonal principle which causes the gall-bladder to empty, and is also free from histamine. For some years clinical work with secretin has been going on in Professor Berglund's Medical Service at St. Erik's Hospital. The work was started and for some time carried on in collaboration with Hammarsten and Ågren.

Methods

An absolute condition for a reliable secretin test is the complete separation of gastric and duodenal secretion. Such separation is by no means a new procedure; it was carried out with some success in Schaefer's laboratory years ago. A further condition is the complete recovery of the whole juice secreted. This seems to have been one stumbling-block in the attempts to measure pancreatic secretion in man in Ivy's laboratory in Chicago. Ågren and I have attempted to solve this technical problem by means of a special double tube and continuous separate delivery of the juices of the stomach and the duodenum as well as the saliva. One bore of the tube ends in the stomach, the other in the duodenum. Each one has several holes in its terminal portion, except for the three inches of the duodenal tube which occupies the pyloric region (Fig. 1). By this procedure the recovery of the juices is so complete and reliable that it is now possible to standardize secretin on normal human subjects as well as on cats.

¹ Received January 4, 1939.

² This is being manufactured at Astra's factories at Södertälje, near Stockholm.

Immediately after the intravenous injection of secretin,³ an abundant flow of pancreatic juice occurs. At the peak of secretion the duodenal contents are colourless. Though secretin stimulates the production of bile, this under normal conditions passes entirely into the gall-bladder. If the gall-bladder has been removed or does not function normally, the duodenal contents

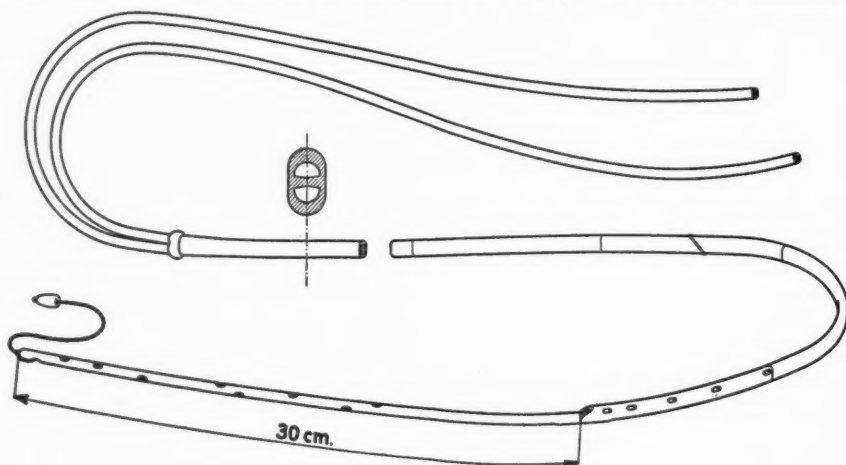


FIG. 1

during the entire course of the test are bile-coloured. This phenomenon, measured by determining the icterus index of the juice, is being used by us as a diagnostic procedure in biliary disease. Colourless duodenal contents correspond in X-ray diagnosis to a normal gall-bladder shadow. Evenly bile-coloured contents correspond to a gall-bladder which fails to show on the X-ray film after the test dye for cholecystography has been given.

During the course of an hour about 150 c.c. of duodenal contents is obtained. Only a small amount of this is bile. The volume and the bicarbonate concentration of the duodenal contents are determined, and the concentrations of diastase, trypsin, and lipase. The enzyme concentrations are expressed in units, obtained from empirical curves or theoretically calculated. From the fractionated duodenal contents one obtains characteristic curves for volume, for bicarbonate, and for enzyme concentrations. The bicarbonate concentration is nearly parallel to the rate of secretion, and in this respect resembles the hydrochloric acid of the gastric juice. The enzymes behave in the opposite way, their concentrations being practically inversely proportional to the rate of secretion. The curves of secretion of the different enzymes run parallel to one another. The behaviour is similar in normal and pathological cases; the difference is of a quantitative order. Thus when it comes to evaluating the function of the pancreas, the concentrations

³ The standard amount of secretin used is one clinical unit per kilo body weight. One clinical unit corresponds to 16 cat units. According to Ågren 1 mg. of the crystalline substance represents an average of 253 cat units.

do not suffice. It is necessary to know the volumes and to calculate the actual amounts of both bicarbonate and enzymes, particularly of the latter. For instance, the amount of diastase during sixty minutes following the injection of secretin equals the concentration of the diastase multiplied by the sixty minutes' volume.

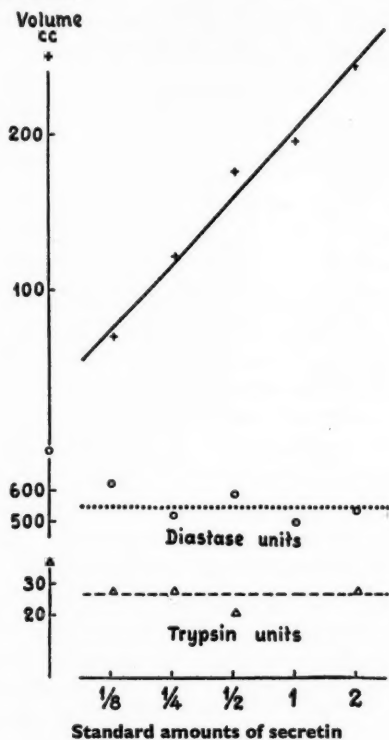


FIG. 2

The Secretin Effect

In analysing the secretin effect one is first struck by the fact that the volume of pancreatic juice is directly proportional to the amount of secretin injected. This is demonstrated in Fig. 2 (the diagonal line) for a series of doses, the largest of which is sixteen times larger than the smallest. The case of the bicarbonate is similar. The behaviour of the enzymes is different, since the amounts secreted are largely independent of the secretin dosage. Immediately after the secretin injection a washing out of pre-formed enzymes takes place, and thereafter their secretion remains more or less constant. It is unlikely that the secretin produces any increased activity within the enzyme-producing cells. In Fig. 2 the dotted and the interrupted horizontal lines represent the diastase and the trypsin respectively.

The behaviour of the enzymes calls for further elucidation. Briefly the

explanation is this: it is the tone of the vagi that regulates the enzyme production, not the humoral stimulation by the secretin. This was demonstrated by Mellanby (1925) in animal experiments and has been fully confirmed in this laboratory by observations on man. When hypoglycaemia is produced by intravenous injection of insulin, and secretin then injected, amounts of enzymes are produced much larger than after secretin alone. A similar effect is obtained from pilocarpine, while atropine causes a decrease

TABLE I

Repeated Secretin Tests on the Same Individual on Different Occasions

| Date. | Volume in c.c. in 60 min. | Amount of diastase in units in 60 min. | Amount of trypsin in units in 60 min. |
|-------|------------------------------|---|--|
| 14.5 | 275 | 878 | — |
| 6.6 | 248 | 863 | 66.8 |
| 21.7 | 248 | 905 | 64.7 |
| 19.8 | 303 | 904 | 69.6 |

of the enzyme production, independently of a small effect upon the volume. In such experiments the rise or fall of the different enzymes is parallel. After ingestion into the duodenum of certain digestive products, an isolated increase of the corresponding pancreatic enzyme may occur. This is in accordance with the teaching of Pavlov, and in man it has been demonstrated by Christiansen (1933) in Denmark. I have been able to confirm these observations in a different way.

Thus we may conceive three different mechanisms co-operating in the stimulation of the pancreas: (1) stimulation by secretin, (2) vagal stimulation, (3) stimulation by the split products of digestion. Whether this third mechanism acts through the vagi has not been determined. Against such an assumption is the fact that a dissociated enzyme production is the result of this mechanism. From the work with the second mechanism, that of vagal stimulation, it seems to follow that the spread of the enzyme values after secretin in normal subjects, at least to some extent, is to be interpreted as an expression of differences in vagal tone. In repeated experiments on different occasions on the same person, insignificant variations only are observed in the amounts of enzymes produced during the same length of time. This suggests that under the conditions of the experiment an individual presents small variations in vagal tone only.

Table I shows four separate tests in one individual. Both the volumes of pancreatic juice and the amounts of enzymes correspond well in the different tests.

The Test

For the diagnostic test the volume collected in one hour is used. Bicarbonate, diastase, trypsin, and lipase are determined. Since these substances are wholly absent from the bile or present in small amounts only (e.g. bicarbonate), admixture of bile does no harm. Neither does the bile affect the enzyme activities.

In the clinical evaluation of the work of the pancreas the bicarbonate and

diastase are of particular importance. Their determination is simple and accurate. The mean error of the diastase method is 2 per cent. With the standard dosage of secretin one gets practically maximal stimulation. Under these conditions the amount of bicarbonate secreted may be looked upon in a rather simple way as the function of two factors only, the mass of pancreatic tissue and its functional capacity. In regard to bicarbonate secretion, the secretin test comes near to the ideal functional test. On the other hand, the amount of enzyme depends upon the following factors: (1) the same mass and functional capacity of the pancreas, and (2) the vagal tone. It is likely that the variations in these two factors are responsible for the distribution curve of the enzymes in normal subjects, which shows a double hump, while the distribution curve for the bicarbonate only shows a single hump. The different mechanisms for bicarbonate and enzymes make the secretin test a double one. This increases its diagnostic significance, but at the same time makes its evaluation difficult. The volume of juice and the bicarbonate content are very constant and not easily disturbed. The enzymes show independent normal variations, in regard to volume, to bicarbonate, and to each other. Further, the enzyme production is the first to suffer when the pancreas is damaged. Among the enzymes the diastase elimination is more easily injured than the others.

When one follows the course of an *acute pancreatitis* by repeated secretin tests, the volume of juice and the amounts of bicarbonate may remain normal throughout the disease, while during the acute stage the enzymes are depressed, but later, during convalescence, return to normal. Among the enzymes the diastase may approach zero, while the trypsin remains within normal limits. This may be referred to as Type I disturbance. While one group of pathological cases shows isolated enzyme disturbances, particularly isolated diastase disturbance, another pathological group shows a correlated diminution of all pancreatic functions, volume, bicarbonate, and enzymes. This may be referred to as Type II disturbance. Combinations of types I and II may exist. Type I is characteristic of acute pancreatitis. The functional disturbance is reversible, and in most cases recovers completely. The pathological basis for the disturbance probably need not be more grave than toxic-inflammatory oedema. Type II may occur in any disease of the pancreas, rarely in acute pancreatitis. The simplest interpretation of this disturbance is a reduction in amount of functioning pancreatic tissue, diffuse or regional. There may be destruction of pancreatic cells from different causes (cirrhosis, necrosis, or carcinoma), or obstruction of pancreatic ducts (by oedema, tumour, or calculus).

The practical diagnostic value of the secretin test is demonstrated by Figs. 3 and 4, and by Table II. Fig. 3 gives the distribution of the amounts of bicarbonate in 41 normal subjects, compared with 25 patients with pancreatitis, three with pancreatic calculi, and four with cancer of the pancreas. The normal bicarbonate elimination during sixty minutes, following the intravenous injection of the standard dose of secretin, presents a mode

of 150 c.c. of 0.1 N bicarbonate solution. As usual with this type of material the values are skew and scattered over a wide range. From the diagnostic point of view the important fact is that the demarcation between low

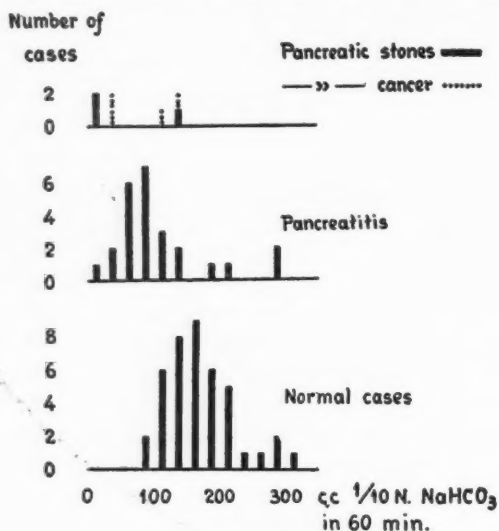


FIG. 3

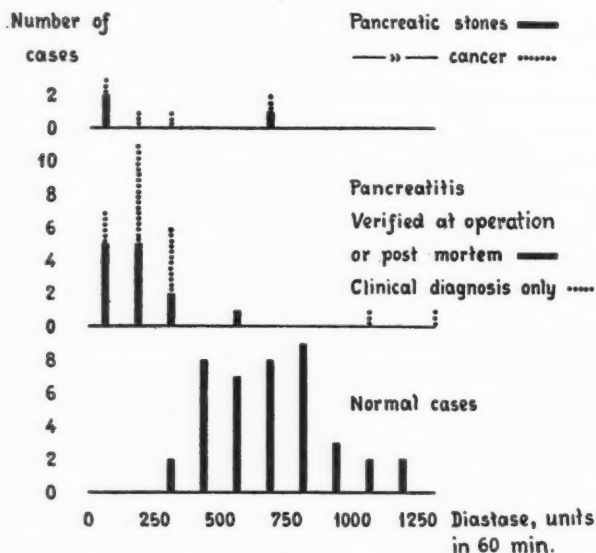


FIG. 4

normal values and pathological subnormal values is definite. A tendency towards subnormal values is clearly demonstrated in the pathological material. Fig. 4 shows in a similar manner the diastase elimination in the

same material. Here it is not feasible to speak about a mean or mode, the values are too evenly scattered over a wide range, with a tendency towards two maxima—a phenomenon mentioned above in discussing the enzyme dependency on the vagal tone. Even here the demarcation towards subnormal values is sharp. Contrary to the case of the bicarbonate, there is a clear distinction between the pathological and the normal material.

The normal material satisfies stringent requirements. Half the number of subjects have not been hospital patients, they are students, nurses, clerks, &c., the other half consists of hospital patients with conditions such as sciatica and fractures. Beyond the normal material in Figs. 3 and 4, a great number of patients with gastric ulcer, achylia, and psychoneuroses have been tested; they all fall within the normal limits. The cases of pancreatitis are divided into those verified by operation or post-mortem examination (full lines), and those where the diagnosis is based on the clinical picture only (dotted lines). In the top section the full and the dotted lines have a different meaning, the dotted line indicating cancer of the pancreas, and the full line stones in the pancreatic duct. The patient with stone and normal function had his calculi in the body of the gland, remote from its head and the duodenum. In the top section only the three cases on the extreme left, two of stones and one of cancer, have had what is commonly called pancreatic fatty stools, bulky and soft. In the pancreatitis material there have been no such cases, though several microscopically have shown fat in abundance and undigested muscle-fibres.

Table II gives the diagnostic results expressed in figures. It is evident that determinations of the diastase are of higher direct diagnostic value than bicarbonate determinations (7 normal, 5 suspected, 22 clearly pathological, for diastase; as against 15 normal, 6 suspected, 11 definitely pathological, for bicarbonate). It is clear even from this first pathological material, which has been examined by the secretin test, that alterations in function can be detected even in chronic pancreatitis, where much of the diagnosis hitherto has of necessity been guess-work. The cases of chronic pancreatitis are diagnosed conservatively. Most of them in the course of a long illness have had acute exacerbations as the immediate cause for coming under observation. The majority of these cases are patients with a history of chronic biliary disease, and in many the gall-bladder has been removed. The acute and chronic biliary material of our surgical service is now being investigated with the secretin test by Mr. Elvin of that service.

Finally, Table III gives the details upon which the diagnoses are based.

Some observations on the external pancreatic function in diabetes mellitus deserve a brief mention. Secretin tests have been done on 22 diabetics. Two had pancreatic calculi, one cancer of the pancreas, and one had been through a very severe acute pancreatitis. Of the remaining 18, none had any other sign of pancreatic disease than the diabetic condition. The diabetics had a lower average bicarbonate elimination than normal, in 10 patients the amounts were significantly lower, in three patients the values

were on the border line of normality. The diastase elimination resembles the bicarbonate. Eight patients showed definitely subnormal values, five border-line values. The low values of diastase do not depend on elevated blood-sugar levels. Special experiments have ascertained this point.

TABLE II

Number of Cases of Pancreatic Disease with Normal or Decreased Function

| Diagnosis. | Total number of cases. | Amount of bicarbonate. | | | Amount of diastase. | | | Amount of bicarbonate or diastase. | |
|--|------------------------|------------------------|---------------------|-------------------|---------------------|---------------------|-------------------|------------------------------------|-------------------|
| | | Normal. | Suspected decrease. | Obvious decrease. | Normal. | Suspected decrease. | Obvious decrease. | Suspected decrease. | Obvious decrease. |
| Acute necrosis of pancreas or acute pancreatitis | 6 | 2 | 1 | 1 | 1 | — | 5 | — | 5 |
| Chronic pancreatitis | 21 | 10 | 4 | 6 | 4 | 3 | 13 | 4 | 13 |
| Lithiasis of pancreas | 3 | 1 | — | 2 | 1 | — | 2 | — | 2 |
| Cystadenoma of pancreas | 1 | — | 1 | — | — | 1 | — | 1 | — |
| Cancer of pancreas | 4 | 2 | — | 2 | 1 | 1 | 2 | — | 3 |
| Total number | 35 | 15 | 6 | 11 | 7 | 5 | 22 | 5 | 23 |

TABLE III

The Basis for the Diagnosis of Pancreatic Disease

Diagnosis not verified at operation or post mortem.

| Diagnosis. | Total number of cases. | Diagnosis verified at operation or post mortem. | Diagnosis based on clinical picture and elevated enzyme values in blood or urine. | Diagnosis based on clinical picture and secretin test. Pancreatitis suspected before secretin test. | Clinically obscure cases. Diagnosis not suspected before secretin test. | | X-ray diagnosis (stones). |
|--|------------------------|---|---|---|---|---------------------|---------------------------|
| | | | | | No function. | Decreased function. | |
| Acute necrosis of pancreas or acute pancreatitis | 6 | 6 | — | — | — | — | — |
| Chronic pancreatitis | 21 | 7 | 7 | 5 | 1 | 1 | — |
| Lithiasis of pancreas | 3 | 1 | — | — | — | — | 2 |
| Cystadenoma of pancreas | 1 | 1 | — | — | — | — | — |
| Cancer of pancreas | 4 | 4 | — | — | — | — | — |
| Total number | 35 | 19 | 7 | 5 | 1 | 1 | 2 |

Case Reports

Three instances may be briefly related, demonstrating the value of the secretin test. Two cases are positive cases with decreased pancreatic func-

tion. The third case is even more important, since a correct differential diagnosis was possible only through the normal result of the secretin test.

Case 1. Acute pancreatitis. St. Erik's Hospital, 4490/36. A-n, A., a woman, aged 62 years. Height 150 cm., weight 62 kg. (about 11 kg. overweight). For four years transient, slight attacks of gall-bladder pain, also dyspeptic symptoms after 'rich' food. On 7.7.1936 attack of another type, vomiting, persistent pain below the left costal margin, radiating to the back at the twelfth rib. On the same day admitted to Sabbatsberg's Hospital under Dr. K. H. Giertz. Temperature 37.9° C., pulse-rate 80. General condition not good. Slightly jaundiced: icterus index (Meulengracht) 18. Marked tenderness and slight resistance in the epigastrium and to the left below the ribs. Urine diastase greatly increased, Wohlgemuth value 8,192. In the stool fatty acid crystals in abundance. After the subsidence of the acute symptoms a secretin test was done on 12.7.1936, five days after the onset of the acute pancreatitis. Blood and urine diastase (Nörby) and blood lipase (Rona) were then normal. The secretin test showed the following values:

| | | |
|--------------------------|------------------------------------|--------------------|
| Patient: volume 156 c.c. | Bicarbonate 117 c.c. of 0.1 N sol. | Diastase 131 units |
| Normal values: | | |
| volume 104-266 c.c. | 82-301 c.c. | 300-1,200 units |

Thus the volume and the amount of bicarbonate were normal, while the diastase only reached about half the lowest normal value.

On July 22 cholecystectomy was performed; the head of the pancreas was hard and swollen. In the surrounding tissue specks of typical fat necrosis were to be seen. A second secretin test was done on 17.8.1936, twenty-six days after the operation. The volume and the amount of bicarbonate were slightly lower than in the first test, 134 and 92 c.c. respectively. The diastase, on the other hand, had increased more than two and a half times and was 342 units, a low normal value.

Summary. This is a typical case of acute pancreatitis, which during the acute stage showed a significant enzyme disturbance of type I. Six weeks after the onset of the pancreatitis the test was normal, though on the verge of a disturbance of type II. The amount of bicarbonate had decreased slightly since the first test. This may or may not indicate slight cirrhosis on the basis of the changes noticed at the operation.

Case 2. Cancer of the pancreas. St. Erik's Hospital, 7742/37. L-m, A. E., labourer, aged 66 years. Height 164 cm., weight 62 kg. No previous gastric symptoms. Five to six weeks before admission to the hospital attacks of pain in the right upper quadrant of the abdomen, radiating to the back and down the front of the right thigh. The pain was intense and lasted a few hours. No vomiting, no chill. Appetite poor, no diarrhoea. Loss of weight. The temperature only slightly raised. The liver was palpable two fingers below the costal margin and tender to pressure. No jaundice, no anaemia. Stools normal. Blood and urine diastase (Nörby), blood lipase (Rona), and blood-sugar normal. Takata's test clearly positive. Blood sedimentation velocity 92 mm. in one hour. X-ray films of the gall-bladder, of the spine, and of the kidneys revealed no lesions. X-ray examination of the stomach showed a narrowing of the prepyloric part and a deformity of the duodenal bulb, changes considered to be due to an ulcer. The secretin test was done on 1.12.1937. Volume 71 c.c.

Bicarbonate 59 c.c. of 0.1 N solution. Diastase 269 units. Trypsin 32 units. Lipase 74 units. The two last values are about 30 per cent. lower than the corresponding lowest normal value.

The patient died on 1.1.1938, one month after the secretin test, with cachexia and cardiac failure. The autopsy revealed a carcinoma in the body of the pancreas, the size of a goose egg. The tail of the gland showed cirrhosis with dilated ducts; the head was normal. Numerous metastases in the liver and the peritoneum. Portal vein thrombosis. Metastatic carcinoma in fifth lumbar vertebra.

Summary. A case in which malignant tumour of the abdomen was suspected from the beginning, but where the localization could not be determined before the secretin test. This showed a disturbance of type II corresponding to the exclusion of a portion of the gland, confirmed at autopsy.

To the question which presents itself as to the sensitiveness of the secretin test no conclusive answer can yet be given. The qualitative disturbance described as type I no doubt is more sensitive in revealing acute changes than type II in demonstrating diminution of parenchyma, as in early cirrhosis of the gland. Thus, one must take care not to exclude pancreatic lesions of this kind, because no type II disturbance is found.

Quite a different situation exists in gross steatorrhoea. Gross steatorrhoea due to pancreatic disease represents a grave functional disturbance in the secretin test shown by marked diminution of all values. Such diminution was also found in pancreatic stone and pancreatic carcinoma. Gross steatorrhoea, however, is also caused by 'malabsorption of fat' (Blumgardt) of an idiopathic type, sometimes known as non-tropical sprue or under other names. Thus, if in gross steatorrhoea the secretin test is normal, the pancreas may be ruled out as the cause, a differential diagnosis of therapeutic importance. Such a case is the last patient to be presented.

Case 3. Intestinal infantilism. St. Erik's Hospital 4550/37. K-d, S. E., aged 29 years, office clerk. Admitted on 5.7.37, discharged on 22.12.37. From earliest childhood had suffered from diarrhoea which had increased in severity during the last seventeen years. Evacuations always voluminous, of light colour, two to five daily. As a child very large and tense abdomen, in later years moderate meteorism. No abdominal pain. Always felt tired. Always thin, but had kept his weight the last few years. In the years 1930 to 1935 he had, every spring, tonic cramps in his hands and forearms with tetany. The cramps came on the slightest effort, and it was difficult for him to carry on his work. Always kept to a restricted diet, 1925 to 1930 so restricted that he developed scurvy. Since 1930 he had eaten more butter and an orange a day. Admitted to one of the medical services of St. Erik's Hospital the first time in May 1935. The abdomen was soft and there was no tenderness. Stools: soft and of light grey or yellow colour. Blood-sugar and urine diastase normal. The blood-calcium 8.4 mg. per cent. X-ray examination of the stomach and duodenum showed a marked alteration of the duodenal loop, interpreted as a duodenitis, possibly with periduodenitis as the cause of the distorted shadow. The peristalsis of the small intestine was accelerated, the main

part of the contrast material being in the large bowel after four hours. Admitted to the hospital repeatedly during the years 1935 and 1936. The condition remained practically unchanged. Further X-ray films of the stomach and intestines gave the same results. No pancreatic calculi were detected. Blood-sugar, urine, and blood diastase, and Rona's test always normal. Mucus was never present in the stools; catalase reaction only slightly positive. Microscopically there was an abundance of fatty acid crystals and fat droplets, sometimes also striated muscle-fibres. Sometimes iodophile substances and bacteria. A glucose tolerance test in March 1936 gave normal values. The return of the blood-sugar to the fasting value occurred in two hours and a quarter. The blood values were normal. X-rays of the gall-bladder in December 1935 and January 1936 and twice in April 1937 failed to visualize the bladder. The patient was transferred to the surgical service of the hospital for cholecystectomy. Before operation a secretin test was done, and this showed the pancreatic juice to be normal both qualitatively and quantitatively. During the entire test the duodenal juice remained colourless, which indicated that the gall-bladder function was normal. Further, the gastric content during the secretin test showed a fair concentration of hydrochloric acid. The proposed operation was not done. Prolonged administration of contrast material for visualizing the gall-bladder resulted in a faint gall-bladder shadow in which no calculi could be detected. After egg-yolk the shadow diminished normally. Going into the history anew, it was found that in the last year the patient's tongue had been sore. In a glucose tolerance test in May 1937, about a year after the previous test, the blood-sugar did not rise above 113 mg. per cent., a type of curve regularly found in sprue. There was also a hypochromic anaemia with 65 per cent. haemoglobin and 4 million red cells.

Summary. A twenty-nine year old hyposthenic male patient with long-standing gross steatorrhoea, a history suggesting tetany and including scurvy, in whom the physical examination revealed a subnormal blood-calcium, but no pathological values for pancreatic enzymes in blood or urine. The normal secretin test settled the differential diagnosis between pancreatic disease and intestinal infantilism (non-tropical sprue) in favour of the latter. It likewise showed the gall-bladder function to be normal, the contrary having been assumed on the basis of repeated X-ray examinations. Further observation confirmed the diagnosis.

Summary

1. Two requirements for a functional test of external pancreatic secretion had to be fulfilled: a pure secretin preparation, which could safely be used on man, and a clinical procedure by which the duodenal juice could be quantitatively recovered without admixture of gastric secretion. The first requirement has been met through the work of Hammarsten and others, the second through the use of a special double tube for the stomach and duodenum.

2. The normal function of the pancreas has been studied. A distinction has been made between the secretory response to secretin, to vagal stimulation, and to the split products of ingested food.

3. A clinical test for pancreatic function is described whose evaluation is based upon the volume of pancreatic juice, its bicarbonate content, and its enzymes. Among the last the diastase possesses the highest functional significance.

4. Normal variability and pathological deviations are presented; two types of pathological tests are distinguished; and clinical instances are given.

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STERNAL PUNCTURE IN THE DIAGNOSIS OF DISEASES OF THE BLOOD-FORMING ORGANS¹

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With Plates 10-12

Historical Introduction

UNTIL seventy years ago the bone marrow was an unexplored and neglected tissue, regarded as having the merely mechanical function of filling the medullary cavity of the bones. Robin in 1849 described the nucleated cells of red marrow (médullocelles) but ascribed to them no specific function, and von Kolliker and Hasse (cit. Segerdahl, 1935), examining the skeleton in cases of arthritis, concluded that the cellularity of the marrow was evidence of an inflammatory process in the bones. Robin had noted the resemblance of the 'médullocelles' to the leucocytes of circulating blood, but it remained for Neumann to show that the bone marrow was, in post-natal life, the site of erythropoiesis (1868) and leukopoiesis (1869). Neumann's contention was supported by Bizzozero (1868) and Claude Bernard (1869) and, although occasional dissentient voices were raised (Robin, 1874; Hayem, 1877; Pouchet, 1879) it soon gained general acceptance. Study of the changes found in the bone marrow in disease rapidly followed, but it was not long before difficulties arose in correlating the changes in the blood *in vivo* with the state of the bone marrow *post mortem*. Dissatisfaction with these anomalous findings led to attempts at obtaining bone marrow for examination from the living patient. Wolff in 1903 devised a method of obtaining marrow from the living animal by opening the medullary cavity of the tibia or femur, and in the same year Pianesi (1903) punctured the femur of a patient and aspirated marrow with a Potain's apparatus. But the pioneer of bone-marrow biopsy was Ghedini who published in 1908 a method of trephining the upper end of the tibia and making sections and smears of the curetted marrow. Later papers (1910, 1911) showed the clinical applications of his method, but, apart from Spuler and Schittenhelm's (1913) report of a case of lymphoid leukosis, Ghedini's technique was little used until 1921. During the past eighteen years a number of authors have employed this means of biopsy (Zadek, 1921, 1922; Caronia, 1922; Kramar and Hensch, 1925; Peabody, 1926, 1927; Löwinger, 1935 a).

Bone-marrow biopsy was simplified by Seyfarth's (1923) introduction of

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a method of trephining the sternum. Designed originally as an alternative to splenic puncture in the diagnosis of malaria and kala-azar, this method consists of trephining the outer lamina of the sternum and removing marrow with a curette. Interest was awakened by Seyfarth's paper and numerous papers on the clinical applications of his technique were published (Morris and Falconer, 1922; Weiner and Kaznelson, 1925; Schilling, 1925; Yamamoto, 1925; Varela, 1930, 1931; Escudero and Varela, 1930, 1932; Barta, 1931; Dameshek, 1931, 1933, 1935, 1937; Custer, 1933, 1936). Sternal trephining demands for its performance the panoply of a major surgical operation and for this reason it has never been generally used. It was this limitation which aroused such interest in Arinkin's (1929) method of sternal puncture. This author punctured the outer lamina of the sternum with a stout needle and made films from the aspirated mixture of blood and bone marrow. During the past few years Arinkin's method, or modifications of it, have been employed extensively, and its clinical utility has been emphasized by Nordenson (1935), Segerdahl (1935), Schulten (1937), Rohr (1937), Mallarmé (1937), Klima (1938), and others. The purpose of the present communication is to analyse the findings in some 250 cases which have been submitted to sternal puncture in the past three years and to determine the diagnostic value of this procedure in diseases of the blood-forming organs. The superiority of sternal trephining over puncture has been stressed by many authors (Dameshek, 1937). By the former method bone marrow is obtained undiluted with blood and with its anatomical relations undisturbed, but for routine use these advantages are outweighed by the ease and simplicity of sternal puncture. A detailed comparison of the two methods is beyond the scope of this paper, which concerns itself only with an attempt to assess the value of sternal puncture.

Practical Considerations

Custer and Ahlfeldt (1932) have shown that the marrow of the sternum remains haemopoietic throughout normal life and that it responds early to stimuli causing hyperplasia; coupled with its accessibility, these facts make it ideal for biopsy. Nordenson (1935) has punctured several bones (sternum, ribs, pelvis) in the same patient and found that the marrow from each is similar qualitatively and in cellularity. Von Domarus (1937) has recorded cases which point to irregularities of distribution of cellular marrow in the sternum, and post-mortem evidence confirming this has been presented by Helpap (1937) and Reiter (1938). General experience shows the rarity of such anomalies and the composition of the sternal marrow may safely be taken as representative of the whole mass of haemopoietic tissue.

The site of election for diagnostic puncture of the sternum is in the body at the level of the third or fourth intercostal space halfway between the midline and the edge of the bone. The reasons for this choice are anatomical: firstly, fusion of the two sternal plates is incomplete in 20 per

cent. of cases, and a central foramen is left in the lower half of the body (Pässler, 1931), or more rarely union in the midline is cartilaginous throughout the length of the bone; secondly, before the age of twenty-five years osseous union between the sternebrae may be incomplete, and bars of cartilage persist at the level of the chondrosternal articulations; finally, the manubrium is occasionally so prolonged as to articulate with the corpus sterni at the level of the third costal cartilage. The manubrium has frequently been punctured (Arinkin, 1929) but is less suitable as aplasia occurs in it earlier than in the body (Pässler, 1931), and the spongiosa is often thin in the centre (Lissitzyn, 1929; Arieff, 1931).



Fig. 1. Salah's sternal puncture needle ($\frac{1}{2}$ natural size)

Many needles have been devised for sternal puncture (Arieff, 1931; Baserga, 1934; Reich, 1934; Klima and Rosegger, 1935; Henning and Korth, 1934; Karavanov, 1936; Rohr, 1937; Mallarmé, 1937; Weller, 1937). They are all essentially similar, consisting of a short strong needle fitted with a stylet and carrying an adjustable stop. In the present series that designed by Salah (1934) and made by Messrs. Allen & Hanbury has been used (Fig. 1). The needle, a 1 c.c. and a 10 c.c. record-fitting all-glass syringe are sterilized by dry heat.

Technique. The patient lies supine with the head supported on one pillow; the skin over the sternum is shaved, if necessary, and cleaned with ether. The skin and subcutaneous tissues over the site chosen for puncture are infiltrated with 2 per cent. novocain and the hypodermic needle driven down until the periosteum is reached, where a generous amount—1 to 2 c.c.—of anaesthesia is injected. After allowing three or four minutes for anaesthesia to become complete, the sternal puncture needle is pushed through the skin and subcutaneous tissues until its point can be felt to touch bone. Then, holding the needle at right angles to the surface of the sternum, a little pressure with a boring movement will cause the point to penetrate the compacta and enter the spongiosa; when the needle will remain upright without being supported it has usually been inserted to a sufficient depth. The stylet is now removed and the 1 c.c. syringe fitted to the needle; as the plunger is withdrawn 'blood' is seen to flow into the barrel. Not more than 0.1 c.c. is aspirated, the syringe is removed, the needle withdrawn and films made on slides from the material remaining in the needle. Occasionally no aspiration can be effected with the small syringe; in these circumstances the greater suction afforded by the 10 c.c. syringe is usually successful, but in about 0.5 per cent. of cases no specimen has been obtainable. A sternal puncture done in this way is almost painless; complaint is made when the needle touches the periosteum prior to the introduction of novocain, and aspiration of the bone marrow is attended by a momentary discomfort, but the operation causes no distress.

The films of the puncture fluid are stained by the May-Grünwald-Giemsa or some similar method, and a complete count of the peripheral blood is made at the time of the puncture. This method is but little different from those described by other authors. Some puncture the manubrium (Arinkin, 1929; Arieff, 1931); Henning and Korth (1934) inject heparinized plasma or normal saline through the puncture needle before aspiration, claiming that they obtain by this procedure marrow elements without admixture of blood. Amprino and Penati (1935) allow the aspirated material to clot; the clot is fixed, embedded in celloidin and in sections from it they claim to find fragments of bone marrow undistorted by the trauma of making smears. Karavanov (1936) has devised a method in which the marrow is curetted through a sternal puncture needle.

Examination of the puncture fluid. The fluid obtained by sternal puncture consists of bone-marrow cells suspended in a variable quantity of blood. The greater the volume of fluid aspirated, the greater the proportion of admixed blood and for this reason not more than 0.1 c.c. is withdrawn. It is clearly important to find some method of assessing the cellularity of the marrow in each case examined, but enumeration of the nucleated cells in the puncture fluid has given such inconsistent results that it has been generally abandoned. Two variables render this figure fallacious: firstly, the dilution with circulating blood, and secondly, the lability of normal bone marrow. Segerdahl (1935) has published nucleated-cell counts on punctures from healthy persons and her mean figures are: Men 75,000 per c.mm. $\sigma = 38,400$ per c.mm. Women 82,700 per c.mm. $\sigma = 41,100$ per c.mm. If the probable limits of normality be taken as plus or minus three times the standard deviation (Yule, 1932), the lower limit in each case falls below zero; thus statistical analysis does not confirm the significance of a numerical count. Greif (1937, 1938) has recently claimed that a cell count is of value, but the limits of normal in his cases are 45,000 and 150,000 per c.mm. These figures agree with Lossen's (1910) post-mortem findings in children of 27,000 to 156,000 per c.mm. The problem has also been studied by Tuschinsky and Kotlarenko (1932) in patients with typhus fever; they found variations of 23,700 to 233,200 per c.mm. between individual counts, and further showed that the greater the quantity of fluid aspirated the lower the nucleated-cell count.

In the present series numerical counts were made in the earlier cases, but the variations were so great that it soon became clear that the figures added nothing of value to the data. In spite of the fallacies inherent in a cell count, there is little doubt that the degree of cellularity of the puncture fluid is of significance in most cases and does reflect roughly the cellularity of the sternal marrow, provided a standard technique is used. For this reason the later preparations have been graded according to cellularity into low (approximately that of a normal blood film); medium (that of the healthy marrow); and high. On this basis a film of low cellularity means a marrow which is considerably poorer in cells than normal or excessive

dilution with circulating blood, and a highly cellular film a marrow of increased cellularity. To strain after greater precision is to attempt to endow the method with an accuracy it cannot possess.

The normal differential cell count. Terminology. Much of the confusion which mars haematological writings can be traced to the abuse of terms. For this reason a note on the vocabulary used in this paper is necessary. So many haemocytophological terms already exist that no excuse can be found for inventing new ones, and the danger of such innovation is illustrated by a recently published Atlas of Haematology (Osgood and Ashworth, 1937). The nomenclature used in the present paper is that of Ferrata (1933), with the modification that his terms 'haemohistioblast' and 'haemocytophoblast' have been abandoned. These omissions have been made partly because of the criticisms of Naegeli (1931) and partly because other writers have used those terms with a different meaning (Vaughan, 1936 *b*). Haemohistioblast, moreover, infers a tissue cell determined exclusively to the generation of haemocytes, and in the minds of most writers there is doubt whether such a cell exists. For these reasons the term 'reticulum cell' is used in conformity with Rohr (1937), Markoff (1937), and others for the primitive undifferentiated mesenchymal cell seen in marrow films. Rohr (1937) describes also lymphoid, plasmacytoid, and phagocytic forms, representing reticulum cells which have undergone differentiation in a direction other than that of the haemocytes.

The myeloid series is subdivided into myeloblast, promyelocyte, and the neutrophil granulocytes into the grades originally suggested by Schilling (1929), of myelocytes and young, band and segmented forms. Eosinophils are classed as myelocytes and segmented forms; and basophils, on account of their rarity, are not subdivided. The lymphoid cells are subdivided into lymphoblasts, prolymphocytes, and lymphocytes. By lymphoblast is meant a lymphoid cell of the same order of maturity as a myeloblast. The monocyte series are classed as monoblasts, promonocytes, and monocytes. Plasma cell is used to include Türk cells and bone-marrow plasma cells as suggested by Naegeli (1931). The term 'reticulum cell' is employed for the undifferentiated mesenchymal cell or haemohistioblast of Ferrata (1933). The classification of the erythrocyte precursors is that of Ferrata and Negreiros-Rinaldi (1914). Thus erythroblast means any nucleated cell of this group while the orthoplastic (normal; definitive) series of erythroblasts are classed as pronormoblast, basophilic, polychromatic, and orthochromatic normoblast, and the dysplastic series as promegaloblast, basophilic, polychromatic, and orthochromatic megaloblast. The problem of the megaloblast is discussed at greater length in a later section.

The term leukaemia is employed in preference to leukaemia. Adami advocated its usage as long ago as 1913 and, in spite of recent criticism by Forkner (1938), it has the value of focusing the attention on the tissue changes rather than on the haematological epiphenomena. Myelosis (myeloid leukaemia) and lymphoid leukaemia are used as descriptive of the two

main varieties of leucosis. Leukaemic, subleukaemic, and leukopenic are used to describe the leucocyte content of the peripheral blood; the first term denotes a leucocyte count of over 20,000 per c.mm., the third one under 7,000 per c.mm. and the second one which falls between these two extremes.

TABLE I

Differential Cell Counts of Sternal Puncture Material from Six Normal Cases.

| Cell | Case | | | | | | Mean. % |
|----------------|--------|--------|--------|--------|--------|--------|------------|
| | 1 % | 2 % | 3 % | 4 % | 5 % | 6 % | |
| Myeloblast | 1.6 | 3.2 | 1.6 | 0.8 | 1.4 | 2.0 | 1.77 |
| Promyelocyte | 3.6 | 6.8 | 4.4 | 2.4 | 3.7 | 6.0 | 4.50 |
| Neutrophil | | | | | | | |
| Myelocyte | 12.8 | 12.8 | 13.6 | 12.8 | 16.3 | 10.0 | 13.05 |
| Young form | 17.6 | 12.8 | 15.2 | 16.4 | 16.4 | 15.8 | 15.70 |
| Band form | 15.2 | 16.4 | 17.2 | 17.6 | 12.4 | 17.2 | 16.00 |
| Segmented | 14.8 | 16.4 | 14.8 | 13.6 | 13.1 | 15.8 | 14.75 |
| Eosinophil | | | | | | | |
| Myelocyte | 2.8 | 2.8 | 2.8 | 2.0 | 2.5 | 0.4 | 2.22 |
| Segmented | 1.6 | 1.6 | 1.2 | 1.6 | 1.3 | 1.6 | 1.50 |
| Basophil | — | — | — | 0.4 | 0.2 | — | 0.10 |
| Lymphocyte | 10.4 | 6.4 | 8.8 | 12.0 | 13.9 | 13.9 | 10.85 |
| Plasma cell | 0.4 | 0.8 | 0.4 | 1.6 | — | 2.0 | 0.87 |
| Monocyte | 1.2 | 0.8 | — | 1.2 | 0.4 | 1.2 | 0.80 |
| Pronormoblast | 0.4 | 0.8 | 0.4 | 0.4 | 0.2 | 0.4 | 0.43 |
| Normoblast | | | | | | | |
| Basophilic | 1.2 | 2.8 | 2.8 | 2.8 | 1.3 | 0.8 | 1.95 |
| Polychromatic | 13.2 | 12.4 | 14.4 | 11.2 | 13.1 | 11.2 | 12.58 |
| Orthochromatic | 3.2 | 2.8 | 0.8 | 3.2 | 4.0 | 2.4 | 2.73 |
| Mitotic | — | 0.4 | — | — | — | — | 0.07 |
| Total | | | | | | | |
| Normoblasts | 18.0 | 19.2 | 18.4 | 17.6 | 18.6 | 14.8 | 17.80 |

The normal differential count. The number of cells counted has varied from 250 to 1,000. In the earlier cases the higher number was counted, but it soon became evident that this was not necessary. No significant variation was found between four counts of 250 cells on different films from the same puncture. The limits of normality are so wide that only gross changes are significant. In Table I are set out differential counts from six cases in which the peripheral blood count was within normal limits. Table II shows the mean normal counts from thirteen authors (Arinkin, 1929; Tempka and Braun, 1932; Holmes and Broun, 1933; Segerdahl, 1935; Nordenson, 1935; Reich, 1935; Young and Osgood, 1935; Roversi and Tanturri, 1935; Rohr, 1935a; Markoff, 1936; Mallarmé, 1937; Vogel, Erf, and Rosenthal, 1937; Klima, 1938) together with the grand mean of these thirteen and the ranges of variation; for comparison the mean from the present six normal cases is inserted. The ranges of counts from sternal trephine preparations from Doan and Zerfas (1927), Escudero and Varela (1932), Dameshek (1935), and Custer (1936) are given so that the degree of dilution with circulating blood may be assessed. Reference to these figures will show the wide variations in the counts on healthy persons and the

approximation of the mean percentages of the six normal cases in this series to those of the published counts. Figures showing the normal ranges in healthy persons have also been published by Debré, Lamy, Sée, and Mallarmé (1936), and Greif (1937), but as mean values are not available they have been omitted from this table. Kato (1937) has recorded counts from normal children from one to fifteen years of age.

In analysing sternal puncture counts most workers have taken the proportion of granulocytes to erythroblasts as an important figure; this is often termed the myeloid-erythroid ratio. Pontoni (1936) has suggested that a more accurate indication of the relation between granulopoietic and erythropoietic activity might be given by the ratio between the percentage of erythroblasts and that of the immature cells of the granulocyte series from myeloblast to young form neutrophil inclusive. This he has called the leuko-erythrogenetic ratio. This ratio has the advantage of eliminating errors due to dilution with circulating blood, but obviously introduces others by discounting the band form and segmented neutrophils in the marrow; however, my experience has shown it to be the more reliable of the two and it has been used in this series. The mean normal from my cases is 1.97 ($\sigma = 0.34$).

Two other methods of analysis are sometimes of use—the estimation of the myeloid and erythroblast maturity dispersions. These are expressed by stating the percentile proportions of myeloblasts, promyelocytes, neutrophil myelocytes, and young forms, taking the sum of the percentage of these cells in the total count as 100. In the erythroblast series the percentage of the total normoblasts, represented severally by pronormoblasts, basophilic, polychromatic, and orthochromatic normoblasts will express the maturity dispersion. For this purpose polychromatic and orthochromatic cells are grouped together. These figures provide a means of assessing the degree of shift in the maturity of the granulopoietic and erythropoietic cells. The mean normal values from my cases are: myeloblast 5.1 per cent., promyelocyte 12.6 per cent., myelocyte 37.2 per cent., young form 45.0 per cent., and pronormoblast 2.5 per cent., basophilic normoblast 10.8 per cent., polychromatic and orthochromatic normoblasts 86.6 per cent. These figures show a close correlation with Pontoni's (1936) findings and with those obtained from sternal trephine material by Escudero and Varela (1932).

STERNAL PUNCTURES IN DISEASE

The Anaemias

1. *Anaemias due to deficiency of iron.* Studies of the metabolism of iron have led to a better understanding of the anaemia of iron deficiency (Hahn, 1937; Heath and Patek, 1937), and under this head may now be grouped a number of anaemias previously regarded as individual entities (Scott, 1938). Iron deficiency anaemia presents itself in the following clinical guises:

TABLE
Normal Sternal Counts

| Cells. | Arinkin, 1929. | Tempka and Braun, 1932. | Holmes and Brown, 1933. | Segerdahl, 1935. | Nordenson, 1935. | Reich, 1935. | Young and Osgood, 1935. | Roversi and Tanturri, 1935. | Rohr, 1935. |
|--------------------------------|----------------|-------------------------|-------------------------|------------------|------------------|--------------|-------------------------|-----------------------------|-------------|
| | % | % | % | % | % | % | % | % | % |
| Myeloblast | 1.7 | 5.1 | 2.4 | 1.3 | 2.1 | 2.0 | 0.6 | 0.3 | 1.3 |
| Promyelocyte | 1.9 | 8.3 | 7.0 | 1.5 | 3.1 | 20.0 | 3.9 | 1.4 | 9.5 |
| Neutrophil myelocyte | 6.6 | 11.4 | | 14.2 | 7.3 | | 1.3 | 15.1 | 6.6 |
| Neutrophil young form | 2.4 | 13.4 | 6.7 | 14.8 | 22.2 | 5.0 | 7.4 | 26.5 | 8.0 |
| Neutrophil band form | 48.0 | 16.4 | 14.0 | 8.3 | 4.4 | 10.0 | 24.1 | 23.1 | 41.0 |
| Neutrophil segmented | | 16.1 | 17.4 | 22.3 | 16.6 | 25.0 | 13.3 | | 17.0 |
| Eosinophil myelocyte | 1.0 | 3.2 | 1.0 | 1.3 | 1.7 | 1.0 | 1.2 | 1.6 | 3.7 |
| Eosinophil segmented | | 2.0 | | 1.7 | 1.3 | | 1.3 | 3.1 | |
| Basophil myelocyte | — | 0.3 | 0.1 | — | 0.1 | — | — | — | 0.4 |
| Basophil segmented | — | | | 0.2 | 0.1 | — | 0.1 | 1.0 | |
| Lymphocyte | 11.9 | 2.6 | 24.9 | 19.5 | 15.7 | 10.0 | 10.4 | 12.6 | 11.0 |
| Plasma cell | — | 0.9 | — | 0.5 | 1.1 | 1.0 | 0.5 | 0.4 | — |
| Türk cell | 0.6 | — | — | — | — | — | — | — | — |
| Lymphoid cell | — | 1.3 | — | — | — | — | — | — | — |
| Monocyte | 5.7 | 0.5 | 9.0 | 2.2 | 1.0 | 1.0 | 2.1 | 1.8 | 1.5 |
| Reticulum and endothelial cell | | 0.7 | — | 0.1 | — | — | 3.2 | — | 7.0 |
| Ferrata cell | — | 2.2 | — | — | 3.4 | — | — | — | — |
| Megakaryocyte | 3.1 | 2.7 | — | — | — | — | — | — | — |
| Disintegrated cells | — | — | — | — | — | — | 22.6 | — | — |
| Primitive cells | — | — | 2.6 | — | — | — | — | — | — |
| Erythroblasts | 12.3 | 12.2 | 12.1 | 12.3 | 18.2 | 25.0 | 14.8 | 12.6 | 30.1 |
| Pronormoblast | 1.4 | — | — | — | 0.4 | 2.0 | — | 0.2 | 4.4 |
| Basophilic normoblast | 16.5 | — | — | — | 1.3 | 8.0 | — | 2.4 | — |
| Polychromatic normoblast | | 4.9 | 6.9 | — | 16.5 | | 12.7 | 4.9 | 9.3 |
| Orthochromatic normoblast | | 7.3 | 5.2 | — | | 15.0 | | 5.1 | 16.4 |
| Mitotic normoblast | — | — | — | — | — | — | — | — | — |
| 'Megaloblast' | — | — | — | — | — | — | 2.1 | — | — |
| Unclassified cells | — | — | — | — | — | — | — | — | — |

* Doan and Zerfas (1927), Escudero and

II

from Various Authors.

| | Markoff, 1936. | Mallarmé, 1937. | Vogel, Erf, and Rosenthal, 1937. | Klima, 1938. | Grand mean. | Maximal-minimal range. | Normal means of present series. | Range of normal sternal trephine counts.* | Cells. |
|-----|----------------|-----------------|----------------------------------|--------------|-------------|------------------------|---------------------------------|---|--------------------------------|
| | % | % | % | % | % | % | % | % | |
| 1-3 | 1.5 | 2.5 | 1.6 | 1.0 | 2.2 | 5.1-0.3 | 1.8 | 0.6-7.6 | Myeloblast |
| 9-5 | 7.5 | 1.5 | 0.1 | 3.0 | 15.2 | 5.2-21.6 | 17.6 | 21.8-42.9 | Promyelocyte |
| 6-6 | 12.0 | 17.5 | 21.5 | 14.0 | | | | | Neutrophil myelocyte |
| 8-0 | 12.5 | 12.0 | | 14.0 | | | | | Neutrophil young form |
| 1-0 | 13.0 | | 30.2 | 11.0 | 48.8 | 38.1-66.0 | 46.5 | 17.5-55.4 | Neutrophil band form |
| 7-0 | 31.0 | 32.5 | 34.0 | 18.0 | | | | | Neutrophil segmented |
| 3-7 | 1.5 | 3.0 | 0.77 | 1.5 | 3.0 | 1.0-5.2 | 3.7 | 0.1-5.6 | Eosinophil myelocyte |
| | 0.4 | 2.0 | 1.33 | 1.1 | | | | | Eosinophil segmented |
| 0-4 | 0.05 | 0.04 | — | — | 0.23 | 0.07-1 | 0.1 | 0.1-0.3 | Basophil myelocyte |
| | 0.05 | 0.04 | 0.07 | — | | | | | Basophil segmented |
| 0-0 | 15.0 | 9.5 | 8.6 | 7.0 | | | | | Lymphocyte |
| | 0.5 | 0.9 | — | 1.0 | 12.8 | 3.5-24.9 | 11.3 | 0-23.5 | Plasma cell |
| | — | — | — | — | | | | | Türk cell |
| 5 | 1.5 | 2.5 | — | 1.0 | | | | | Lymphoid cell |
| 0-0 | 1.0 | — | 0.25 | 0.5 | 3.31 | 0.25-9.0 | 0.8 | 0-4.0 | Monocyte |
| | — | — | — | — | | | | | Reticulum and endothelial cell |
| | 0.05 | 0.06 | 0.2 | — | | | | | Ferrata cell |
| | — | — | — | — | | | | | Megakaryocyte |
| | — | — | — | — | | | | | Disintegrated cells |
| 1 | 13.06 | 16.0 | 29.48 | 26.5 | 19.0 | 12.1-30.1 | 17.8 | 8.6-40.0 | Primitive cells |
| 4 | 0.01 | 6.0 | | 1.5 | | | | | Erythroblasts |
| | | | 7.1 | | | | | | Pronormoblast |
| 3 | 2.5 | | | 7.0 | | | | | Basophilic normoblast |
| | | 10.0 | 22.6 | | | | | | Polychromatic normoblast |
| 4 | 10.55 | | | 18.0 | | | | | Orthochromatic normoblast |
| | — | — | — | 0.7 | | | | | Mitotic normoblast |
| | — | — | 0.14 | — | | | | | 'Megaloblast' |
| | — | — | 3.1 | — | | | | | Unclassified cells |

Varela (1932), Dameshek (1935), Custer (1936).

- (1) Hypochromic anaemia of infants.
- (2) Chlorosis.
- (3) Hypochromic anaemia of pregnancy.
- (4) Hypochromic anaemia following overt blood loss.
- (5) Hypochromic anaemia of hepato-lienal fibrosis.
- (6) 'Idiopathic' hypochromic anaemia.

Knowledge of the bone-marrow changes in these anaemias was scanty until the introduction of sternal puncture, and even since then they have attracted little attention. This anaemia is the commonest of all disorders of haemopoiesis, and the bone marrow demands more consideration than it has been accorded. Kaznelson, Reimann, and Weiner (1929) and Witts (1930) described an increase in red marrow in two cases at post-mortem examination. Barta (1931), Weiner and Kaznelson (1925), and Dameshek (1931) report their findings with sternal trephining as a hyperplastic marrow with great proliferation of normoblasts. Sternal punctures are recorded by Chevallier and Ely (1934), von Jagič and Klima (1935, 1937), Henning (1935), Segerdahl (1935), Markoff (1936), and Rohr (1937). All these authors describe the changes briefly and often superficially. Erythropoiesis is stated to be abnormally active, but proceeding along normal lines. The most careful study is that of Stodtmeister (1937), who, by repeated punctures of the same patients, has shown that the reticulocytosis which follows administration of iron is accompanied in the marrow by an increase in the percentage of erythroblasts. As the blood picture returns to normal the erythroblast percentage falls again until complete normality of blood and bone marrow is reached.

Present material. Twenty-three cases of iron deficiency anaemia have been examined; the majority of these were examples of 'idiopathic' hypochromic anaemia, in some there was a history of gross pathological blood loss, and two were cases of chlorosis. In all cases the anaemia showed no spontaneous improvement during a control period of a week, but was subsequently cured by treatment with iron. In 20 cases sternal puncture was performed before treatment was instituted, and in three after the response to iron had started.

The detailed findings from these cases are set out in Table III. Before treatment all cases showed similar changes. The cellularity of the marrow was high, and there was a relative increase in erythroblasts roughly proportional to the degree of anaemia. In Fig. 2 the leuko-erythrogenetic ratio is plotted against the haemoglobin content of the peripheral blood² and the relation between the severity of the anaemia and the erythroblast percentage is well shown. All the erythroblasts are of the orthoplastic series, and the predominant cell is characteristic of this type of anaemia; it is a small and mature polychromatic normoblast with an irregular and jagged cell-outline and only a small rim of slate-grey cytoplasm around the pyknotic nucleus.

² Throughout this paper, 100 per cent. haemoglobin is equivalent to 18.5 per cent. oxygen capacity.

TABLE III

Sternal Puncture Counts in 23 Cases of Iron-deficiency Anaemia.

| <i>Case.</i> | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|-----------------------------|------|------|------|------|------|------|------|------|------|------|------|------|
| Haemoglobin per cent. | 54 | 43 | 43 | 42 | 29 | 20 | 37 | 49 | 40 | 20 | 40 | 48 |
| Cellularity | + | ++ | ++ | + | ++ | ++ | + | + | ++ | + | ++ | + |
| Myeloblast | 1.6 | 2.8 | 1.6 | 2.8 | 1.2 | 0.8 | 1.6 | 1.6 | 0.6 | 1.0 | 0.8 | 1.2 |
| Promyelocyte | 5.2 | 3.2 | 3.2 | 9.8 | 2.8 | 3.6 | 5.6 | 2.0 | 3.4 | 2.8 | 1.2 | 3.2 |
| Neutrophil | | | | | | | | | | | | |
| Myelocyte | 12.4 | 13.6 | 12.4 | 12.0 | 8.4 | 5.6 | 9.6 | 12.8 | 16.1 | 6.0 | 10.4 | 8.0 |
| Young form | 12.4 | 18.0 | 10.8 | 10.4 | 13.2 | 8.4 | 12.8 | 11.2 | 11.6 | 5.2 | 14.4 | 10.8 |
| Band form | 12.0 | 14.8 | 8.8 | 5.4 | 13.2 | 9.8 | 13.6 | 13.6 | 16.7 | 16.2 | 11.6 | 11.2 |
| Segmented | 8.0 | 6.8 | 8.0 | 7.6 | 13.6 | 8.4 | 14.4 | 11.2 | 14.1 | 13.6 | 8.4 | 18.4 |
| Eosinophil | | | | | | | | | | | | |
| Myelocyte | 0.4 | 1.2 | 2.4 | 1.4 | 0.8 | 0.4 | 0.8 | 2.0 | 0.9 | 1.0 | 0.4 | 0.8 |
| Segmented | 0.8 | 0.4 | 0.4 | 0.4 | 0.4 | 1.2 | 0.8 | 4.0 | 0.6 | 0.2 | — | 1.2 |
| Basophil | — | — | — | 0.2 | 0.4 | — | 0.4 | — | 0.1 | 0.2 | — | 0.4 |
| Lymphocyte | 12.0 | 6.8 | 8.8 | 7.4 | 6.8 | 8.0 | 6.8 | 18.4 | 3.5 | 13.8 | 4.4 | 13.6 |
| Plasma cell | — | 0.8 | 0.4 | — | — | — | — | 0.8 | — | — | 0.4 | 0.4 |
| Monocyte | 0.4 | — | 0.4 | 0.4 | 0.8 | 0.8 | 0.4 | 0.8 | — | 0.2 | — | 1.6 |
| Reticulum cell | — | — | — | — | — | — | — | — | — | — | — | — |
| Pronormoblast | 0.8 | 0.4 | 0.8 | 1.2 | 1.2 | 1.6 | 0.4 | — | 1.2 | — | 1.2 | 1.2 |
| Normoblasts | | | | | | | | | | | | |
| Basophilic | 4.0 | 6.4 | 2.8 | 7.6 | 5.2 | 10.0 | 5.6 | 3.2 | 5.2 | 1.6 | 5.6 | 4.4 |
| Polychromatic | 27.6 | 22.4 | 38.4 | 27.4 | 30.0 | 34.0 | 24.4 | 16.8 | 21.4 | 32.1 | 34.0 | 22.4 |
| Orthochromatic | 2.4 | 2.4 | — | 4.0 | 2.0 | 7.2 | 2.4 | 1.2 | 3.6 | 5.3 | 7.2 | 1.2 |
| Mitotic | — | — | 0.8 | — | — | 0.4 | 0.4 | — | — | 0.8 | — | — |
| Leuko-erythro-genetic ratio | 0.91 | 1.19 | 0.65 | 0.83 | 0.67 | 0.35 | 0.89 | 1.30 | 1.01 | 0.38 | 0.56 | 0.78 |

TABLE III (continued)

| <i>Case.</i> | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21* | 22* | 23* |
|-----------------------------|------|------|------|------|------|------|------|------|------|------|------|
| Haemoglobin per cent. | 49 | 30 | 40 | 39 | 67 | 53 | 33 | 58 | 60 | 70 | 60 |
| Cellularity | + | + | + | + | + | ++ | + | + | + | + | ++ |
| Myeloblast | 0.8 | 3.2 | 1.6 | 1.2 | 1.2 | 1.2 | 2.0 | 0.8 | 1.2 | 3.6 | 2.0 |
| Promyelocyte | 1.2 | 3.2 | 1.6 | 2.0 | 3.2 | 2.8 | 2.4 | 2.8 | 2.4 | 6.6 | 3.6 |
| Neutrophil | | | | | | | | | | | |
| Myelocyte | 8.4 | 7.2 | 8.0 | 13.6 | 10.8 | 8.8 | 7.6 | 10.0 | 9.2 | 16.8 | 7.2 |
| Young form | 14.0 | 8.8 | 13.6 | 14.8 | 15.2 | 16.0 | 15.2 | 14.4 | 16.8 | 14.0 | 8.0 |
| Band form | 16.4 | 12.0 | 10.0 | 18.4 | 15.2 | 15.2 | 12.4 | 14.8 | 17.2 | 6.6 | 10.8 |
| Segmented | 20.4 | 13.4 | 5.2 | 10.4 | 10.4 | 12.4 | 7.2 | 14.8 | 14.4 | 10.0 | 14.8 |
| Eosinophil | | | | | | | | | | | |
| Myelocyte | 2.0 | 1.2 | 0.8 | 2.0 | 1.6 | 2.4 | 0.8 | 2.8 | 0.4 | 1.5 | 2.4 |
| Segmented | 2.4 | 0.4 | 0.4 | 0.8 | 0.4 | 1.6 | 0.4 | 2.0 | 0.4 | 0.7 | 0.4 |
| Basophil | — | — | — | — | 0.4 | — | — | — | — | — | — |
| Lymphocyte | 15.2 | 12.4 | 11.2 | 3.2 | 6.8 | 14.0 | 10.0 | 5.2 | 9.6 | 5.2 | 17.2 |
| Plasma cell | — | — | — | — | 2.0 | — | 1.2 | 0.4 | 0.4 | — | 0.4 |
| Monocyte | 0.4 | 0.4 | 0.8 | 0.4 | — | 0.4 | — | 1.6 | — | — | 0.8 |
| Reticulum cell | — | 0.4 | 0.4 | — | 0.4 | 0.4 | — | 0.4 | — | 0.2 | — |
| Pronormoblast | 0.8 | 0.8 | 0.4 | 0.8 | — | 1.6 | 0.4 | 0.4 | 0.4 | 1.2 | 0.8 |
| Normoblasts | | | | | | | | | | | |
| Basophilic | 0.8 | 2.8 | 1.6 | 1.6 | 0.8 | 2.0 | 3.2 | 1.6 | 3.6 | 7.2 | 11.6 |
| Polychromatic | 16.0 | 30.8 | 38.4 | 30.0 | 24.8 | 20.0 | 32.0 | 27.6 | 22.8 | 20.6 | 20.8 |
| Orthochromatic | 0.8 | 2.0 | 2.8 | 0.8 | 2.4 | 1.2 | 4.8 | 0.4 | 0.4 | 5.6 | 0.4 |
| Mitotic | 0.4 | 0.8 | 0.8 | — | 0.8 | 0.4 | 0.4 | 1.2 | 0.8 | — | 0.8 |
| Leuko-erythro-genetic ratio | 1.30 | 0.60 | 0.62 | 0.95 | 1.06 | 1.14 | 0.67 | 0.90 | 1.06 | 1.18 | 0.60 |

[Cases marked with an asterisk were examined after the institution of treatment.]

Occasional cells of this type occur in many sternal puncture preparations, but when they dominate erythropoiesis, iron deficiency is to be inferred. Many writers (Schulten, 1937; Rohr, 1937; Segerdahl, 1935; and others) have stated that there is nothing characteristic in the bone-marrow findings in 'idiopathic' hypochromic anaemia. This is indeed true, but they have

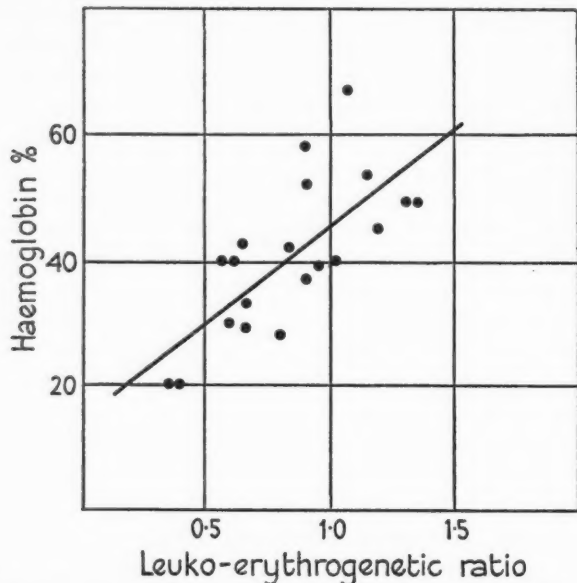


FIG. 2. Scatter diagram showing relation of leuko-erythrogenetic ratio to haemoglobin percentage in iron-deficiency anaemia

failed to appreciate that this complaint is but one of a large group of anaemias due to deficiency of iron. All iron-deficiency anaemias show the same bone-marrow changes, provided the complicating factor of infection be absent. These changes are typical, and a diagnosis of iron-deficiency anaemia may be made on the sternal puncture findings with assurance.

Granulopoiesis shows no significant deviation from the normal in this anaemia. Dameshek (1931) has described a diminution in the leukogenetic cells and in megakaryocytes, but this is not confirmed by other authors, and in this series the low percentage of granular cells appears to be due only to the increase in erythroblasts and does not reflect a hypoplasia. The maturity dispersion is within the limits of normal. Rohr (1937) has described large and atypical young form neutrophils, and these have been present in one or two of the present cases.

With the institution of treatment, quantitative and qualitative changes occur in the erythroblasts. Stodtmeister (1937) has shown that the percentage of erythroblasts increases steadily after the administration of iron until a peak is reached which corresponds in time with the maximal reticulocytosis in the peripheral blood. In the present series no serial punctures

have been done, but three cases were punctured after iron treatment was started. In these three the leuko-erythrogenetic ratio was considerably lower than the haemoglobin level would have led one to anticipate; an observation which conforms with Stodtmeister's findings. The qualitative changes consist of an increase in size of the erythroblasts with a higher percentage of basophilic and immature polychromatic forms than in the untreated cases. The normoblasts no longer show the irregularity of cell outline, and they cannot be distinguished from normal cells.

2. *Anaemias due to deficiency of the 'liver complex'.* The hypothesis of Castle (1933) has now gained general acceptance as the most probable explanation of the pathogenesis of Addisonian pernicious anaemia, although recent work suggests that it errs on the side of simplicity. His concept of the extrinsic dietary factor and the intrinsic factor secreted by the gastric epithelium interacting to produce a substance which is essential for normal haemopoiesis (liver complex) offers a ready solution to the problem of the other conditions resembling Addisonian anaemia. Thus the following group of anaemias may be recognized as probably dependent upon deficiency of the liver complex.

- (1) Addisonian pernicious anaemia.
- (2) Tropical megalocytic anaemia.
- (3) Pernicious anaemia of pregnancy.
- (4) Megalocytic anaemia associated with steatorrhoea (sprue, Gee's disease, lacteal obstruction, and gastro-jejuno-colic fistula).
- (5) Megalocytic anaemia associated with organic disease of the alimentary tract (gastric carcinoma, gastric operations, intestinal strictures).
- (6) Megalocytic anaemia associated with *Dibothriocephalus latus* infestation.

In addition to these conditions admission to the group has been sought for two others: achrestic anaemia (Wilkinson and Israëls, 1935; Israëls and Wilkinson, 1936) in which an inability to use the liver complex is postulated; and the macrocytic anaemia of chronic disease of the liver in which a loss of storage capacity of the principle is suggested (Wintrobe and Schumacker, 1933). Wilkinson and Israëls' observations lack confirmation, and I have seen no cases to which their description would apply. No evidence has yet been produced which shows that the macrocytic anaemia of hepatic disease is in reality due to defective storage or other interference with the function of the liver complex, and the condition is discussed in a later section.

The megaloblast question. The problem of the megaloblast is one of the vexed questions of haematology at the present time; to those not interested in haemocytology this controversy may appear sterile and unimportant. This is far from true, and upon the megaloblast question depends the interpretation of the pathology of Addisonian and allied anaemias. For this reason a brief summary of the position is necessary before considering the changes in the bone marrow in these anaemias.

Ehrlich (1880) first distinguished two kinds of erythropoiesis, the normal post-natal type (normoblastic), and a type present in the foetus, but in

extra-uterine life found only in Addisonian anaemia (megaloblastic). Later these cells were described more fully and the differences between the two types reiterated by Ehrlich and Lazarus (1898). The first doubts about this hypothesis were raised by Pappenheim (1911), who had at first supported Ehrlich, but later claimed that megaloblasts might in some cases form normoblasts. Maximow (1909, 1910) introduced confusion by using 'megaloblast' to mean the most primitive erythroblast of normal marrow; later, swayed by the excellent paper of Ferrata and Negreiros-Rinaldi (1914) he discontinued this abuse of the term, but in 1927 he reverted to it, explaining that his megaloblast was not the same as the megaloblast of Ehrlich. Confusion was further confounded by Doan, Cunningham, and Sabin (1925), who defined the megaloblast as the first generation of cells of the erythrocyte series of foetal and adult life, a position which is clearly untenable, as foetal and adult erythropoiesis are dissimilar (Ferrata, 1933; Knoll, 1932). This misconception is still widely current in America, and Doan and Zerfas (1927), Sabin (1928), Custer (1933), and Young and Osgood (1935) all describe megaloblasts in normal bone marrow.

At the present time the megaloblast is regarded as a normal constituent of bone marrow and the normal precursor of the normoblast by the majority of American and by some English writers (Whitby and Britton, 1935). On the other hand, German (Naegeli, 1931; Schulten, 1937), French (Mallarmé, 1937), Italian (Ferrata, 1933; Storti, 1937 *b*), Scandinavian (Segerdahl, 1935; Nordensen, 1935), and Swiss (Rohr, 1935), as well as some American (Jones, 1934) and English (Turnbull, 1936) authors consider the megaloblast to be a pathological cell which is found only in anaemias due to deficiency of the liver complex; in these anaemias two types of erythropoiesis occur, megaloblastic and normoblastic, which are separate and distinct. The argument is not, as at first appears, a terminological quibble, but is concerned with whether the cell which dominates erythropoiesis in Addisonian anaemia is the normal precursor of the erythrocyte or whether it is a pathological dysplastic cell occurring only in disease. Ehrlich's contention that a reversion to foetal erythropoiesis takes place in Addisonian anaemia was strongly upheld by Naegeli (1931), but was doubted by Maximow (1927) and Turnbull (1936). Livadas (1933) and Zanaty (1934 *b*) have described cytological differences between the two types of erythropoiesis which throw further doubt on their identity.

From the study of the material at my disposal I have formed certain views on the megaloblast problem. In Addisonian anaemia a dysplastic erythropoiesis occurs, and a series of erythroblasts can be followed as they develop from the reticulum cell to the megalocyte; these cells are never seen in normal marrow and constitute the megaloblastic series described by Ferrata (1933) and others. The following stages are recognizable in their development: promegaloblast, basophilic, polychromatic, and orthochromatic megaloblasts. Megaloblasts, in my view, never give rise to normoblasts. The dominant cells of the bone marrow in Addisonian anaemia are

promegaloblasts and basophilic megaloblasts: these are never seen except in anaemias of this group. The more mature polychromatic megaloblasts have not the same specific significance and may occur in leukosis and leuko-erythroblastic anaemia (Vaughan, 1936 *a*; Jones, 1938). The orthochromatic megaloblast may be indistinguishable from the analogous normoblast of large size.

Addisonian pernicious anaemia. William Pepper of Philadelphia described the microscopical changes in the bone marrow in Addisonian anaemia in 1875, interpreting the condition as one closely allied to leukosis. In the next year Cohnheim (1876) suggested that the marrow of this disease showed a reversion to the foetal type of erythropoiesis. The earliest comprehensive account of the marrow histology was published by Geelmuyden in 1886, and knowledge of post-mortem pathology was summarized in a classical paper by Ellerman (1920). Zadek (1921, 1922) recorded the results of examination of marrow obtained from living patients in remission and relapse, and described the change from megaloblastic to normoblastic erythropoiesis which occurred with the onset of remission. His findings were confirmed by Peabody (1927). The introduction of Seyfarth's technique (1923) gave an additional stimulus to bone-marrow biopsy, and accounts of the changes in Addisonian anaemia have been published by Weiner and Kaznelson (1925), Fontana (1928), Isaacs (1930 *b*), Escudero and Varela (1932), Dameshek (1935), and Dameshek and Valentine (1937). The sternal puncture findings have been recorded by Tempka and Braun (1932), Holmes and Broun (1933), Reich (1934), Nordenson (1935), Rohr (1935 *a, b*, 1938), Tempka (1935), Segerdahl (1935), Mallarmé (1937), Storti (1937 *b*), Klima (1938), and many others.

Present material. Twenty-five cases of Addisonian anaemia have been studied. In all, daily reticulocyte counts and haemoglobin estimations have been made prior to and following sternal puncture, and before treatment was instituted; in this way it was possible to determine whether a spontaneous remission had occurred or was about to occur when the puncture was done. Now that this anaemia is treated so energetically with liver the frequency of spontaneous remissions is often forgotten; they are, however, of great importance when cases are used to assess the efficacy of liver or stomach preparations, particularly when the reticulocytosis rather than the gain in haemoglobin is taken as an index.

In 15 cases punctures were done where no spontaneous remission occurred and before treatment was started. Details of these cases are given in Table IV. The picture depends to some extent upon the severity of the anaemia, but the correlation is not nearly so exact as in iron deficiency anaemia, although Penati and Saita (1938) claim that a relation can be established. The cellularity of the marrow is high, and there is a great increase in erythroblasts, both the orthoplastic and dysplastic series being represented, although the latter predominate. Of the normoblast series only polychromatic and orthochromatic forms are commonly seen; these make up less than a third of the total erythroblasts in most cases. The characteristic

TABLE IV

Sternal Puncture Cell Counts in 25 Cases of Addisonian Pernicious Anaemia.

| Case. | 1 ¹ | 2 ¹ | 3 ¹ | 4 ¹ | 5 ¹ | 6 ¹ | 7 ¹ | 8 ¹ | 9 ¹ | 10 ¹ | 11 ¹ | 12 ¹ | 13 ¹ |
|-----------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|-----------------|-----------------|-----------------|-----------------|
| Haemoglobin per cent. | 30 | 48 | 47 | 46 | 25 | 61 | 33 | 31 | 30 | 88 | 42 | 30 | 41 |
| Myeloblast | 0.8 | — | 1.0 | 1.5 | 3.5 | 2.5 | — | 1.2 | 2.0 | 1.2 | 1.5 | 2.4 | 0.5 |
| Promyelocyte | 2.4 | 2.0 | 1.6 | 2.5 | 3.3 | 2.5 | 3.3 | 2.5 | 1.0 | 2.8 | 4.0 | 7.2 | 0.5 |
| Neutrophil | | | | | | | | | | | | | |
| Myelocyte | 5.6 | 5.6 | 4.5 | 10.0 | 4.3 | 15.0 | 6.0 | 7.6 | 4.4 | 8.4 | 8.0 | 7.6 | 10.0 |
| Young form | 12.0 | 6.2 | 2.5 | 2.5 | 4.9 | 4.5 | 7.0 | 9.6 | 3.2 | 8.4 | 5.0 | 11.2 | 3.0 |
| Band form | 11.2 | 10.2 | 4.5 | 5.0 | 6.5 | 6.0 | 9.0 | 7.2 | 2.6 | 8.4 | 16.0 | 14.0 | 1.0 |
| Segmented | 29.6 | 7.0 | 12.8 | 3.0 | 19.7 | 7.5 | 5.0 | 6.8 | 7.6 | 8.8 | 17.0 | 10.8 | 6.0 |
| Eosinophil | | | | | | | | | | | | | |
| Myelocyte | 4.8 | 1.2 | 1.0 | 1.5 | 0.1 | 1.0 | 1.5 | 3.2 | 1.8 | 0.4 | 1.5 | 0.8 | 2.5 |
| Segmented | 2.4 | 0.8 | 0.9 | 0.5 | 0.5 | 0.5 | 1.5 | 1.6 | 2.8 | 1.6 | 0.5 | 0.8 | 0.5 |
| Basophil | — | 1.0 | — | — | — | — | — | — | 0.2 | — | — | 0.4 | — |
| Lymphocyte | 10.4 | 9.0 | 3.2 | 4.0 | 32.9 | 3.5 | 2.0 | 11.2 | 16.6 | 17.2 | 7.0 | 4.8 | 1.0 |
| Plasma cell | — | — | — | — | — | — | — | — | 1.2 | — | — | — | — |
| Monocyte | — | 2.0 | — | 2.5 | — | — | — | — | — | — | 1.5 | — | 1.0 |
| Reticulum cell | 0.8 | 2.0 | — | — | — | — | — | — | 0.4 | — | — | — | — |
| Pronormoblast | — | — | — | — | — | — | — | — | — | — | — | — | — |
| Normoblasts | | | | | | | | | | | | | |
| Basophilic | — | — | — | — | 0.7 | 0.6 | — | 0.4 | 1.0 | 0.8 | — | — | — |
| Polychromatic | 2.4 | 14.8 | 10.9 | 10.7 | 2.9 | 5.1 | 4.1 | 3.6 | 7.4 | 10.8 | 3.4 | 4.0 | 9.1 |
| Orthochromatic | 0.8 | 3.2 | 2.0 | 2.1 | 0.5 | 1.2 | 0.6 | 1.6 | 15.2 | 19.2 | 2.3 | 4.8 | 1.3 |
| Promegaloblast | 2.4 | 4.8 | 6.1 | 10.7 | 7.0 | 9.1 | 12.9 | 15.6 | 5.8 | 0.8 | 10.3 | 8.4 | 9.1 |
| Megaloblasts | | | | | | | | | | | | | |
| Basophilic | 6.4 | 11.1 | 23.1 | 20.6 | 10.2 | 20.5 | 20.1 | 16.0 | 12.2 | 3.2 | 9.9 | 8.8 | 18.2 |
| Polychromatic | 7.2 | 13.8 | 23.8 | 22.0 | 2.0 | 16.5 | 20.1 | 8.0 | 5.4 | 4.0 | 9.8 | 9.2 | 24.0 |
| Orthochromatic | 0.8 | 3.7 | 1.4 | 2.1 | 0.3 | 1.7 | 4.1 | 3.6 | 0.4 | 2.8 | 3.0 | 4.0 | 0.7 |
| Mitotic erythroblasts | — | 1.6 | 0.7 | 2.8 | — | 2.3 | 4.1 | — | — | 1.2 | — | 1.6 | 2.6 |

TABLE IV (continued).

| Case. | 14 ¹ | 15 ¹ | 16 ² | 17 ² | 18 ² | 19 ³ | 20 ³ | 21 ³ | 22 ³ | 23 ³ | 24 ⁴ | 25 ⁴ |
|-----------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Haemoglobin per cent. | 56 | 28 | 72 | 33 | 62 | 64 | 38 | 59 | 35 | 48 | 102 | 92 |
| Myeloblast | 2.4 | — | 1.7 | — | 0.6 | — | 0.4 | 3.0 | 0.8 | 0.4 | 3.5 | 0.8 |
| Promyelocyte | 2.0 | 0.4 | 4.8 | 6.4 | 3.8 | 5.0 | 2.8 | 1.5 | 3.6 | 1.2 | 6.0 | 3.2 |
| Neutrophil | | | | | | | | | | | | |
| Myelocyte | 4.8 | 5.2 | 6.0 | 2.0 | 10.8 | 4.4 | 5.2 | 6.0 | 16.8 | 11.6 | 16.0 | 11.9 |
| Young form | 10.0 | 7.6 | 8.0 | 6.0 | 8.2 | 5.6 | 8.8 | 5.0 | 16.8 | 16.8 | 16.0 | 13.4 |
| Band form | 9.2 | 4.8 | 7.8 | 2.0 | 12.2 | 9.4 | 10.0 | 3.0 | 4.0 | 16.0 | 20.0 | 9.2 |
| Segmented | 4.8 | 19.6 | 11.3 | 2.8 | 7.7 | 15.6 | 16.8 | 11.5 | 2.0 | 10.8 | 9.0 | 20.1 |
| Eosinophil | | | | | | | | | | | | |
| Myelocyte | 0.4 | 2.4 | 0.3 | — | 0.4 | 0.6 | 0.8 | — | 1.2 | 1.2 | 2.5 | 0.8 |
| Segmented | 1.2 | 0.4 | 0.7 | — | 0.5 | 1.4 | 2.0 | — | 0.8 | 0.4 | 1.5 | 1.7 |
| Basophil | 0.4 | — | — | — | — | — | — | — | — | — | — | 0.6 |
| Lymphocyte | 11.2 | 16.4 | 20.8 | 8.8 | 9.3 | 21.2 | 19.2 | 5.0 | 5.2 | 8.8 | 2.0 | 32.4 |
| Plasma cell | — | 0.4 | — | — | — | — | — | — | 1.2 | — | — | — |
| Monocyte | — | 0.4 | 0.2 | — | 0.1 | — | — | 1.0 | — | 0.4 | 2.5 | 0.1 |
| Reticulum cell | 3.6 | 4.0 | 0.2 | — | — | — | — | — | 0.8 | — | — | — |
| Pronormoblast | — | — | — | — | 1.2 | — | — | — | — | 1.2 | 0.4 | — |
| Normoblasts | | | | | | | | | | | | |
| Basophilic | — | — | 3.5 | 4.4 | 5.8 | 0.8 | — | — | 0.4 | 4.4 | 2.5 | — |
| Polychromatic | 6.0 | 2.0 | 8.7 | 30.8 | 19.9 | 20.8 | 2.0 | 17.9 | 2.8 | 10.8 | 14.3 | 3.4 |
| Orthochromatic | 5.6 | 1.6 | 11.2 | 12.4 | 14.0 | 11.8 | 10.8 | 1.9 | 2.4 | 2.0 | 3.2 | 2.4 |
| Promegaloblast | 4.4 | 8.4 | 0.5 | 0.4 | 0.2 | 0.2 | 2.8 | 2.6 | 3.6 | — | — | — |
| Megaloblasts | | | | | | | | | | | | |
| Basophilic | 7.6 | 9.6 | 1.7 | 8.2 | 0.7 | 1.2 | 6.0 | 6.4 | 12.0 | 0.8 | — | — |
| Polychromatic | 19.6 | 12.8 | 6.0 | 12.8 | 3.8 | 1.8 | 2.4 | 32.6 | 20.0 | 10.0 | — | — |
| Orthochromatic | 6.4 | 3.6 | 1.0 | 1.2 | 0.2 | 0.6 | 6.4 | 2.6 | 3.2 | 2.4 | — | — |
| Mitotic erythroblasts | 0.4 | 0.4 | — | 2.8 | — | — | 0.8 | — | 2.4 | 0.8 | 0.6 | — |

¹ Cases 1 to 15 untreated and during relapse.² Cases 19 to 23 during spontaneous remission.³ Cases 16 to 18 during therapeutic remission.⁴ Cases 24 and 25 after anaemia has been repaired.

feature of the film is the large number of promegaloblasts and basophilic megaloblasts; they often occur in groups and frequently show mitotic figures. Polychromatic megaloblasts are plentiful and the majority are immature; their orthochromatic derivatives are less common. Reticulum cells are often increased, and as Jones (1935) has pointed out, their development into promegaloblasts can often be followed; in fact, many of the characteristics of the megaloblast nucleus are shared by that of the reticulum cell.

The changes in leukopoiesis are less profound. In the peripheral blood nuclear hypersegmentation of the neutrophils has long been recognized as characteristic, and the 'macropolycyte' described by Cooke (1925) is frequently seen. Love (1932) has also shown that anisocytosis of the neutrophils exists in the peripheral blood. These changes have their counterpart in the alterations in the granulopoietic cells of the bone marrow. Myeloblasts are usually scanty and promyelocytes and myelocytes commonly predominate, although in many instances young-form neutrophils are plentiful. Giant myelocytes and young forms are common, and nuclear segmentation begins at an abnormally early stage; it may on occasion be seen in the promyelocytes or even in mature myeloblasts. Condensation of the nuclear chromatin, toxic granulation, and vacuolation are common, and many cells give the impression that the maturation of the nucleus has outstripped that of the cytoplasm. These changes, although less flamboyant, are as characteristic as the disturbance of erythropoiesis (Jones, 1936, 1937).

Alterations in the megakaryocytes are reported by several authors (Rohr, 1937; Dameshek and Valentine, 1937, and others). They are stated to include diminution in number, nuclear hypersegmentation, and abnormal granulation. In the present material these cells have been seen only rarely, but they have not shown any definite qualitative abnormality.

Changes in remission. Similar changes occur in spontaneous remission and in those induced by treatment with liver. It has been shown by Rohr (1937) that arsenic therapy does not produce this specific change, but is followed only by an increase in the number of mitotic figures in the megaloblasts. Five cases have been examined during various phases of spontaneous, and three during therapeutic, remission; two have been punctured when the blood picture had returned to normal. The findings confirm Rohr's (1937) views of the cytological changes in remission. The earliest change is an increase in the rate of maturation of the megaloblastic series; promegaloblasts and their basophilic descendants become scanty and finally disappear, while the polychromatic megaloblasts increase in number and maturity. At a later stage most of these cells have disappeared. There is at no time any suggestion that the primitive dysplastic cells mature to form normoblasts; they diminish and are replaced by polychromatic and orthochromatic megaloblasts before the normoblast increase takes place. The process appears to consist of rapid ripening of the existing megaloblasts without the subsequent appearance of more of their precursors. A little

later there is a great increase in normoblasts; numerous basophilic forms are seen at the beginning of the process, but later polychromatic normoblasts predominate. The increase reaches a maximum at the time of the peripheral reticulocyte crisis when the total erythroblast percentage is higher than at any other time. Following this stage there is a gradual fall in the total percentage of erythroblasts, and dysplastic cells disappear from the marrow. By the time the peripheral blood picture has returned to normal the bone marrow has also become normal. Storti (1937 *b*) has found that orthoplastic has completely ousted dysplastic erythropoiesis by the time of the reticulocyte crisis, but this has not been true of the present series of cases. However, no megaloblasts can be found in the bone marrow of patients whose anaemia has been completely repaired. During remission changes occur also in the granulopoietic system. There is a rapid maturation of the abnormal myelocytes and young forms, and their places are taken by normal cells.

Summary. The changes in the bone marrow in Addisonian anaemia affect all its cellular elements. Erythropoiesis is mainly dysplastic and is characterized by the appearance of abnormal cells the majority of which are primitive; leukopoiesis shows a less striking disturbance, but again abnormal cells are present. In remission the primitive abnormal cells rapidly mature and a normoblastic hyperplasia follows their disappearance. Finally the bone marrow becomes indistinguishable from that of health.

These findings which correspond with those recorded by the majority of workers in this field, are of interest in relation to the pathogenesis of Addisonian anaemia. It is widely held that the liver complex is necessary for the maturation of the 'megaloblast to the normoblast', and that the condition is characterized by an 'arrest of maturation'. In the author's view this hypothesis is no longer tenable, for the megaloblast never gives rise to the normoblast and the cytological changes consist of a hyperplasia of primitive dysplastic erythroblasts—a condition histologically analogous to leukopenic myelosis.

Other anaemias due to deficiency of the liver complex. Data concerning other anaemias of this group are scanty. Where reports are available the bone-marrow changes are stated to be identical with those of Addisonian anaemia. This is true of tropical megalocytic anaemia (Fairley, Bromfield, Foy, and Kondi, 1938), sprue (Mackie and Fairley, 1929; Kassirsky, 1932), and pernicious anaemia of pregnancy (Heilbrun, 1936). In the present series two cases of megalocytic anaemia associated with idiopathic steatorrhoea and one with sprue have been examined; in all three cases the changes were indistinguishable from those of Addisonian anaemia, and Rohr's (1936) results support this.

3. *Aplastic anaemia (panmyelophthisis).* Aplastic anaemia or panmyelophthisis is a condition resulting from a progressive decrease in the cellular elements of the bone marrow; the ultimate result of this process is an acellular fatty marrow. Certain causes of panmyelophthisis, such as the

administration of arsenic and X-irradiation, are recognized and it is likely that under the head of 'idiopathic' (cryptogenetic) panmyelophthisis several different conditions are included (Rohr, 1937). The term 'aplastic anaemia' has been robbed of any precise meaning it may have had by its indiscriminate use in American haematological writings (Thompson, Richter, and Edsall, 1934; Rhoads and Miller, 1934).

Fourteen cases of panmyelophthisis (Table V) have been studied in this series and they fall into the following groups.

(i) *Panmyelophthisis arising from known toxic agents.* Benzene (Hamilton, 1931, 1934), radiotherapy (Rohr, 1937), organic arsenical compounds (McCarthy and Wilson, 1932), and gold (Dameshek, 1934) have been recognized as causing aplasia of the marrow. In the present series there is one case (11/3) where an aplastic blood picture resulted from the administration of Stovarsol; sternal puncture early in the disease showed a marrow of low cellularity. During the recovery phase, some months later, the cellularity was still reduced; the erythroblast percentage was low and no megakaryocytes could be found, but in both the erythroblast and granular series the more primitive forms were present in a higher proportion than usual. This finding has been interpreted by some as an arrest of maturation, but it is as readily explicable on the assumption that the earliest sign of recovery is the appearance of the more primitive cells. The effect of radiotherapy is shown by a case of Hodgkin's disease where after four exposures to the thoracic spine the sternal puncture findings suggested a complete marrow aplasia.

(ii) *Cryptogenetic panmyelophthisis.* Thirteen cases in the present series fall into this group. In general there is no agreement upon the classification of such cases, but these examples fall into three apparently distinct types.

(a) *Acute panmyelophthisis with normocytic anaemia.* This is the condition generally termed 'idiopathic aplastic anaemia' which was first described by Ehrlich in 1888 and later renamed 'aleukia haemorrhagica' by Frank (1915). Sternal puncture findings are recorded by Rohr (1937), Klima (1938), Benhamou, Nouchy, and Cohen-Solal (1937), and others. Five cases of this type have been examined; in all the anaemia was orthochromic and normocytic, in all there was neutropenia and thrombocytopenia. Regenerative phenomena such as reticulocytosis, erythroblastosis and a shift to the left of the neutrophils, were never observed in the peripheral blood. All five cases died with rapidly progressive unremitting anaemia; in one case (19/2) the duration of the disease was seven months, in the others it was less.

Sternal puncture findings in all five cases were similar. The cellularity of the preparations was greatly reduced and in the unstained film considerable amounts of fat could be seen with the naked eye. The differential counts (Table V) showed a low percentage of erythroblasts and granulocytes with a proportionate increase in lymphocytes. No megakaryocytes were seen. In one case (19/2) the erythroblast percentage was not reduced,

TABLE

Sternal Puncture Counts

| Case. | a 19/4 | a 18/11 | a 19/11 | a 14/4 | a 19/2 | b 11/3 | c 7/3 | c 13/7 | c 6/3 | d 4/3 |
|----------------|-----------|------------|------------|-----------|-----------|-----------|----------|-----------|----------|----------|
| Reticulum cell | — | — | 1.3 | 1.2 | — | 1.6 | — | — | 2.4 | — |
| Myeloblast | — | 0.1 | 0.7 | — | 0.9 | 5.6 | 2.4 | 1.6 | 0.8 | 2.8 |
| Promyelocyte | 1.2 | 2.1 | 1.2 | 0.4 | 2.0 | 11.6 | 4.8 | 6.0 | 4.0 | 9.6 |
| Neutrophil | | | | | | | | | | |
| Myelocyte | 2.4 | 4.0 | 1.2 | 6.8 | 8.5 | 13.6 | 5.6 | 9.2 | 22.4 | 16.0 |
| Young form | 1.4 | 4.2 | 1.2 | 5.6 | 6.8 | 9.6 | 4.8 | 13.2 | 24.0 | 10.8 |
| Band form | 1.4 | 6.3 | 6.0 | 6.0 | 8.1 | 9.6 | 4.8 | 17.6 | 10.4 | 9.6 |
| Segmented | 1.4 | 12.0 | 9.6 | 8.0 | 4.1 | 9.2 | 6.4 | 23.2 | 0.8 | 15.2 |
| Eosinophil | | | | | | | | | | |
| Myelocyte | — | 0.5 | — | 0.4 | 0.2 | 4.0 | 1.6 | 2.4 | 1.6 | 0.8 |
| Segmented | 0.2 | — | — | 0.8 | 0.4 | 4.4 | 0.8 | 0.4 | 1.6 | 2.8 |
| Basophil | — | — | — | — | — | — | — | — | — | 0.8 |
| Lymphocyte | 84.8 | 68.4 | 73.2 | 65.2 | 45.9 | 22.0 | 57.6 | 20.4 | 9.6 | 18.8 |
| Plasma cell | — | — | 2.0 | 2.0 | — | — | 0.8 | 0.4 | — | 0.8 |
| Monocyte | 0.2 | 2.0 | 3.5 | 1.6 | 0.6 | 2.0 | — | 0.4 | 0.8 | — |
| Megakaryocyte | — | — | — | — | — | — | 0.8 | — | — | — |
| Pronormoblast | — | — | — | — | — | 0.4 | 0.8 | — | — | — |
| Normoblasts | | | | | | | | | | |
| Basophilic | 0.4 | — | — | — | 2.1 | 2.4 | 5.6 | 0.8 | 0.8 | 1.6 |
| Polychromatic | 2.4 | 0.2 | 0.4 | 0.6 | 14.6 | 3.2 | 5.6 | 3.6 | 16.8 | 7.6 |
| Orthochromatic | 2.8 | — | 1.3 | — | 5.6 | 0.8 | 3.2 | 0.4 | 4.0 | 2.8 |

a = acute normocytic panmyelophthisis.

b = panmyelophthisis following 'Stovarsol'.

c = chronic normocytic panmyelophthisis.

d = atypical case with 'aplastic blood picture'.

(The cellularity in all these puncture films was greatly diminished.)

although the cellularity of the films was so low that the erythroblast content of the bone marrow must have been greatly diminished. Unfortunately, in this case no autopsy was permitted, but in the other four fatty aplasia of the marrow was found *post mortem*.

(b) *Chronic panmyelophthisis with normocytic anaemia*. Three cases have been observed to which this description applies. In all, anaemia was only of moderate severity, and the haemoglobin percentages varied from 71 to 48. Granulocytopenia was such a marked feature in two of the patients that they had been termed 'chronic agranulocytosis'. Moderate thrombocytopenia was present. Thus there was a reduction of all the elements normally formed in the bone marrow. In one patient (6/3) recurrent staphylococcal skin infection without suppuration was the presenting symptom; he also showed slight splenomegaly. Sternal puncture preparations were of low cellularity and showed a reduction of granulocytes and erythroblasts. In the case with staphylococcal skin infection, post-mortem examination showed the marrow to be almost acellular, apart from occasional islets of erythroblasts. The other patients are still alive.

Chronic panmyelophthisis of this type has not been accorded recognition, although some cases reported as chronic agranulocytosis are probably of the same nature. From the sternal puncture findings in these three cases it seems likely that a chronic process of unknown aetiology producing a pro-

TABLE
CountsV
in Panmyelophthisis.

| d 4/3 | Case. | ^e 6/9 | | ^e 7/9 | | ^e 7/7 | | ^e 3/8 | | ^e 6/8 |
|----------|----------------|---------------------|------|---------------------|------|---------------------|------|---------------------|------|---------------------|
| — | Count | 1 | 2 | 1 | 2 | 1 | 2 | 1 | 2 | 1 |
| 2.8 | Cellularity | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 |
| 9.6 | Reticulum cell | — | 1.6 | — | — | — | — | 0.8 | — | — |
| 16.0 | Myeloblast | — | 3.2 | 0.4 | 0.4 | 1.2 | 0.4 | 2.0 | 0.8 | — |
| 10.8 | Promyelocyte | 2.8 | 4.0 | 1.6 | 2.4 | 4.4 | 0.8 | 3.6 | 6.0 | 4.8 |
| 9.6 | Neutrophil | — | — | — | — | — | — | — | — | — |
| 15.2 | Myelocyte | 12.8 | 11.2 | 5.6 | 2.4 | 12.4 | 3.2 | 9.2 | 10.4 | 13.6 |
| — | Young form | 15.6 | 10.4 | 6.0 | 2.8 | 14.0 | 4.8 | 15.2 | 11.6 | 14.4 |
| 0.8 | Band form | 20.8 | 4.8 | 9.2 | 4.4 | 17.2 | 8.0 | 13.6 | 14.4 | 6.8 |
| 2.8 | Segmented | 6.4 | 4.8 | 7.2 | 11.6 | 8.4 | 16.4 | 6.4 | 4.8 | 3.2 |
| 0.8 | Eosinophil | — | — | — | — | — | — | — | — | — |
| 18.8 | Myelocyte | 0.4 | 0.8 | 0.4 | — | 1.2 | — | — | 0.4 | 1.6 |
| 0.8 | Segmented | — | — | — | 0.8 | 1.6 | — | — | — | 0.4 |
| — | Basophil | — | — | — | — | — | — | — | 0.4 | — |
| — | Lymphocyte | 23.6 | 46.4 | 44.8 | 58.8 | 11.6 | 61.2 | 23.2 | 21.6 | 9.2 |
| — | Plasma cell | — | — | — | 0.4 | — | — | 0.4 | — | — |
| — | Monocyte | 0.4 | 6.4 | 2.4 | 1.6 | 2.8 | 0.8 | 2.8 | 0.4 | 1.6 |
| 1.6 | Pronormoblast | — | 0.8 | — | — | 0.4 | — | 0.8 | 0.4 | — |
| 7.6 | Normoblasts | — | — | — | — | — | — | — | — | — |
| 2.8 | Basophilic | 0.8 | 0.8 | — | 2.0 | 1.6 | 0.4 | 1.2 | 4.0 | 3.2 |
| — | Polychromatic | 6.8 | 5.6 | 17.6 | 12.0 | 19.2 | 2.4 | 15.2 | 21.2 | 25.2 |
| — | Orthochromatic | 9.6 | — | 3.2 | 0.4 | 3.6 | 1.6 | 5.6 | 2.8 | 15.2 |
| — | Mitotic | — | — | — | — | 0.4 | — | — | 0.4 | — |

e = chronic macrocytic panmyelophthisis.

(Cellularity: 0 = greatly diminished, 1 = approximately that of a normal sternal puncture film, 2 = greatly increased.)

gressive diminution in bone-marrow cellularity must be recognized, in which granulocytopenia rather than anaemia may characterize the peripheral blood.

(c) *Chronic panmyelophthisis with macrocytic anaemia.* Five cases have been investigated to which this title may be applied. They have been the subject of detailed study by Dr. J. F. Paterson who will publish elsewhere a full description of the condition. All five cases showed macrocytic anaemia, neutropenia, and thrombocytopenia. Regenerative phenomena were often present. Such cases run a protracted course, being liable to spontaneous remissions. When anaemia is severe macrocytosis is slight, but when a remission occurs it reappears. Thus in one case when the haemoglobin was 41 per cent. the mean erythrocyte diameter was 7.9μ with 16.2 per cent. macrocytes; eleven months later the haemoglobin percentage was 78, mean diameter 9.35μ , macrocytes 84.4 per cent. The anaemia does not respond to liver or to iron, but large blood transfusions often induce remissions lasting many months. Two cases have died four and six years after the onset of symptoms; the remainder are in fair health after periods varying from three to six years.

In four cases the sternum was punctured twice and in the fifth only once. In the two fatal cases the earlier punctures showed a moderate cellularity,

while later ones showed it to be low. In one case it was low on both occasions and in another it appeared to have increased a little after two years. The differential counts show a decrease in the more mature granulocytes and, in the progressive cases, an increasing reduction of erythroblasts. Megakaryocytes are seldom seen. Erythropoiesis shows remarkable changes; in remission it appears active, but two types of erythroblast can be traced from the basophilic forms downwards. One is the typical normoblast and the other differs from it only by virtue of its greater size. In the remission phase these abnormally large normoblasts can be found in the basophilic, polychromatic, and orthochromatic groups; in the phase of relapse, where the total erythroblast percentage is reduced, only orthochromatic forms are seen. Megaloblasts are never found. In one case only was an autopsy obtained, and in that the bone marrow showed complete aplasia; trephining of the sternum four years previously had shown an active erythropoiesis with numerous large normoblasts.

The probable interpretation of these findings is that the change in the bone marrow in this condition is a slowly progressive panmyelophthisis, but that remissions in the process occur; erythropoiesis is in part abnormal and characterized by giant normoblasts which give rise to the macrocytes so frequently present in the blood. Remission is accompanied by increased proliferation of these giant normoblasts with consequent increase in macrocytosis; relapse is associated with their disappearance and a fall in the mean erythrocyte diameter. It seems doubtful whether these large cells have a specific significance for they are seen in many cases of macrocytic anaemia associated with hepatic cirrhosis or uraemia, but they are never so large or so plentiful as in this anaemia. This type of erythropoiesis is also recorded by Schartum-Hansen (1937) and Zanaty (1937).

These cases conform closely to the description given by Chevallier (1936) of 'l'anémie maligne intermédiaire'. He noted the prolonged course with remissions, the tendency of the colour index to rise with improvement and fall during relapse, and the striking response to blood transfusion. Gandy and Baize (1930) in a post-mortem examination of one such case found fatty aplasia of the marrow. Cases probably of this type have been reported by Williams (1926), Holbøll (1929), Brugsch (1932), and Osato, Hashimoto, and Takigawa (1931, 1935), and the existence of this condition explains the cases often recorded in the past as 'pernicious anaemia becoming aplastic'. These cases also present similarities to the 'achrestic anaemia' described by Wilkinson and Israëls (1935); these authors, however, state that a megaloblastosis of the bone marrow occurred in their cases.

Atypical cases. Two cases have been examined which clinically had the characteristics of 'aplastic anaemia', but which could not be placed in any of the groups described. One (4/3) had an apparently hypoplastic marrow but, on contracting a fatal streptococcal infection of the throat, his leucocytes rose to 24,000 per c.mm. and post-mortem examination showed a highly cellular marrow with a predominance of promyelocytes and myelo-

cytes. The second, a woman, was found to have a severe anaemia during the latter half of pregnancy; the blood picture was normocytic and accompanied by neutropenia and thrombocytopenia, but regenerative phenomena were present. Sternal puncture showed a practically acellular marrow, and, although blood transfusion restored her health and her blood picture to normal, sternal punctures repeated on three occasions have shown acellular films. It is possible that some local abnormality in the sternum accounts for these findings, as in the case of von Domarus (1937).

4. *Haemolytic anaemias. Familial haemolytic icterus.* The main characteristics of the bone marrow in this condition have been known since the early reports of Vaquez and Aubertin (1908), Oettinger (1908), Gandy and Brulé (1909), and Guizzetti (1912) on the post-mortem findings. These authors all stressed the great increase in red marrow and the normoblastic hyperplasia. Tibial trephining was carried out by Escudero and Varela (1932) in five cases; the marrow was hyperplastic, but granulopoiesis appeared as active as erythropoiesis. By Seyfarth's method Weiner and Kaznelson (1925) found marked normoblastic hyperplasia. The reports of sternal puncture all agree: there is a great increase in erythroblasts, which may form 50 to 75 per cent. of the cells in the puncture films, but there appears to be little correlation between the erythroblast percentage, the degree of anaemia, or the peripheral reticulocytosis (Löwinger, 1935 *b*; Schulten, 1937; Mallarmé, 1937; Rohr, 1937; de Weerd, 1938; Klima 1938). Erythropoiesis is recorded as being orthoplastic, but Tötterman (1936) reported a case in which megaloblasts were present in small numbers, and Turnbull (1936) described similar changes *post mortem*. The maturity dispersion of the erythroblasts is usually normal, but Klima (1938) has found an increase in primitive forms in occasional cases. Micronormoblasts and naked nuclei abound (Markoff, 1936; de Weerd, 1938), and mitoses are frequent. The marrow reticulocyte percentage is said to exceed that of the blood by Pokrowsky (1929) and de Weerd (1938), but Rohr (1937) and Ungricht (1938) have recorded the reverse. Jones (1935) has shown that formation of pronormoblasts directly from reticulum cells is often demonstrable.

Four cases of familial haemolytic icterus are included in this series. The findings are tabulated below (Table VI) and agree closely with those reported by other writers. Granulopoiesis is normal, and no correlation seems to exist between the degree of erythropoietic activity and the peripheral blood picture. There is no change in the erythroblasts which foreshadows the spherocytosis of the erythrocytes.

Other haemolytic anaemias. Similar changes occur in other types of haemolytic anaemia. Four cases have been studied; the first is an example of the Marchiafava-Micheli syndrome previously reported (Scott, Robb-Smith, and Scowen, 1938), the second, haemolytic anaemia complicating Hodgkin's disease as described by Davidson (1932), and the third and fourth are cases of unknown aetiology. The findings are set out in Table VII.

5. *Macrocytic anaemia associated with hepatic disease.* An anaemia

TABLE VI
Findings in Four Cases of Familial Haemolytic Icterus.

| Peripheral blood. | | | Bone marrow. | | | | | |
|--|------------------------|-----------------------|--------------------------------|---|---------------------------|-------------------------------------|---|-----------------------------|
| Erythro- cytes in millions per c.mm. | Haemo- globin %. | Reticulo- cytes %. | Total erythro- blasts %. | Leuko- erythro- genetic ratio. | % of total erythroblasts. | | | |
| | | | | | Pronormo- blast. | Baso- philic normo- blast. | Poly- chromatic and ortho- chromatic normo- blast. | Mitotic normo- blast. |
| 4.72 | 96 | 9.4 | 42.25 | 0.43 | 3.6 | 12.5 | 83.9 | 0.6 |
| 3.39 | 71 | 15.2 | 67.6 | 0.20 | 4.4 | 10.8 | 84.8 | 3.1 |
| 1.62 | 29 | 14.4 | 53.0 | 0.52 | 3.9 | 14.0 | 82.1 | 3.4 |
| 1.01 | 20 | 37.8 | 51.4 | 0.44 | 5.3 | 17.6 | 77.1 | 4.1 |

TABLE VII
Findings in Four Cases of Haemolytic Anaemia.

| | | | | | | | | |
|------|----|------|------|------|-----|------|------|-----|
| 2.20 | 60 | 7.0 | 43.0 | 0.47 | 2.2 | 15.4 | 82.4 | 3.0 |
| 1.60 | 20 | 15.0 | 58.2 | 0.32 | 1.7 | 9.6 | 88.7 | — |
| 3.92 | 70 | 12.3 | 48.0 | 0.40 | 3.3 | 14.8 | 81.9 | — |
| 1.59 | 30 | 24.4 | 53.2 | 0.23 | 4.5 | 12.0 | 82.7 | 0.8 |

characterized by macrocytosis and a raised colour index was first observed in association with cirrhosis of the liver by Babonniex and Tixier in 1913. More recently papers on the subject have been published by Wintrobe and Schumacker (1933), van Duyn (1933), Wright (1935), and others, and the suggestion has been made that deficient storage of liver complex in the damaged organ might give rise to a deficiency of the principle. Castle and Minot (1936) have shown the fallacies of this hypothesis. Numerous reports on the marrow changes have been made (Rossier, 1932; Döhnert and Tischendorf, 1937; Fiessinger and Laur, 1937; Fiessinger, Dupuy, and Laur, 1937; Schulten, 1937; Tischendorf, 1938*b*). Naegeli (1931) found a diminished cellularity but orthoplastic erythropoiesis, and other workers agree with the latter conclusion but find varying grades of normoblastic hyperplasia. Isaacs (1935*a*) alone has found the 'number of cells in the megaloblast stage significantly increased', but it is clear from this quotation that he is abusing the term megaloblast. Stasney and Higgins (1936) produced cirrhosis in albino rats by inhalation of carbon tetrachloride; a macrocytic anaemia resulted, but the bone marrow showed only a normoblastic hyperplasia.

In cases of cirrhosis of the liver it is difficult to be certain that haemorrhage has not occurred even when a macrocytic anaemia is present. Thus the picture may often be blurred by an iron deficiency. In three cases where there was a macrocytic anaemia and no evidence of blood loss the cellularity of the marrow was not increased. The differential cell counts showed a reduction in the total erythroblast percentage, but erythropoiesis was orthoplastic; many of the polychromatic normoblasts were abnormally large. The findings suggested that erythropoiesis was depressed.

6. *Anaemia with chronic renal failure and chronic infection.* Parsons and Ekola-Strolberg (1933) have studied the anaemia of chronic nitrogen retention and have concluded that it is due to depression of the bone marrow. The anaemia is commonly normocytic, although sometimes a slight macrocytosis is present. Löwinger (1938) and Nordenson (1938) have found that sternal puncture usually gives a cell-poor marrow with a low percentage of erythroblasts; these are orthoplasic and have a normal maturity dispersion. Three cases in this series show changes such as they describe, findings which support the suggestion of depression of erythropoiesis as the cause of the anaemia. A similar change has been found in four cases of chronic infection with anaemia. In these cases no blood loss had taken place and the anaemia was normocytic.

Reticulosis and Reticulosarcoma

The many conditions resulting from progressive hyperplasia or neoplasia of the blood-forming organs may be grouped under these two heads; the main representatives of the first group are the leukoses (leukaemia) and Hodgkin's disease, but a number of less common reticuloses are gradually becoming recognized (Scott and Robb-Smith, 1936; Robb-Smith, 1938). The reticulosarcomata include lymphosarcoma and myelomatosis as well as the 'reticulum-cell' or 'retothel' sarcomata.

The Leukoses

1. *Myelosis* (myeloid leukaemia). Myelosis occurs in four main clinical-haematological forms, chronic leukaemic, chronic subleukaemic, acute leukaemic, and leukopenic. Less common variants such as eosinophilic myelosis are occasionally seen.

Chronic leukaemic myelosis presents such a characteristic clinical and haematological picture that examination of the bone marrow as an aid to diagnosis is unnecessary. Nevertheless there are numerous reports of the changes which occur, and it was in this disease that puncture of the sternum was first performed in life (Mosler, 1865). Escudero and Varela (1930, 1932) and Weiner and Kaznelson (1926) have recorded the findings with Seyfarth's technique as a great increase in cellularity of the marrow with a differential count closely resembling that of the blood. Similar observations by means of sternal puncture have been made by Sonnenfeldt (1928), Tempka and Braun (1932), Barta (1933), Nordenson (1935), Segerdahl (1935), Merwe (1936), and Mallarmé (1937). Klima (1938) has described changes in maturation of the granulocytes with premature appearance of specific granulation, but Schulten (1937) concludes that the sternal puncture findings are not specific and are similar to those found in some infections. Von Jagić and Klima (1937) and Young and Osgood (1935) believe them to have a diagnostic value.

Ten cases of chronic leukaemic myelosis are included in the present series.

The changes are similar to those described by other authors, and consist of a great increase in cellularity with a differential count running parallel with the blood, but at a slightly less mature level. The erythroblast percentage is much lowered, but it is impossible to determine whether this reflects an absolute reduction; Jaffé (1933) is of the opinion that the erythropoietic

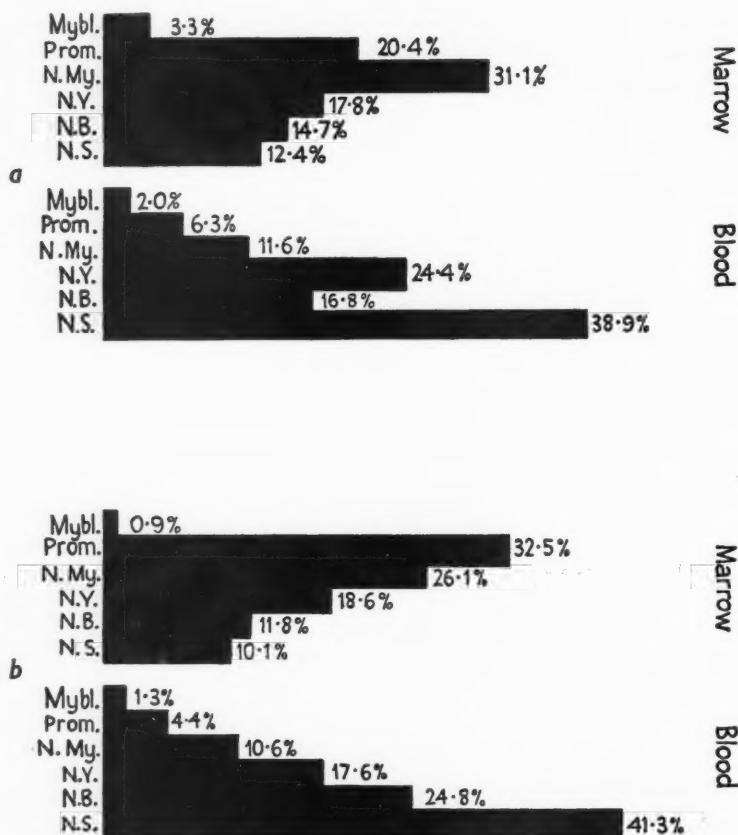


FIG. 3. Histogram showing maturity dispersion of granular cells in blood and bone marrow in two cases of chronic leukaemic myelosis

tissue is not diminished in amount. The relation between the sternal puncture and peripheral blood counts in two cases is shown in the histogram (Fig. 3). An increase in megakaryocytes as noted by Klima (1938) has not been observed in the present cases. In one instance a patient whose blood showed a preponderance of mature neutrophils had a sternal puncture count in which promyelocytes and myelocytes predominated (Fig. 3 (b)). One case of chronic erythromyelosis (a combination of polycythaemia rubra vera with leukaemic myelosis) has been studied, and the sternal puncture findings resembled those of chronic leukaemic myelosis except for a high proportion

of normoblasts, an unusual number of which were basophilic. In another case sternal puncture was done during the terminal phase, when the peripheral leucocytes numbered 8,000 per c.mm., with 77 per cent. myeloblasts. Puncture yielded highly cellular films and a differential count of 97 per cent. myeloblasts. A similar instance has been recorded by Escudero and Varela (1930).

It must be concluded that sternal puncture is seldom, if ever, necessary for the diagnosis of chronic leukaemic myelosis, but in my experience the characteristic changes have not been found in any other condition.

Chronic subleukaemic myelosis. Cases to which this term may be applied have been described by Hickling (1937), but he makes no distinction between this condition and myelosclerosis, a conclusion which I cannot endorse. Sternal puncture or trephining materially assists this differential diagnosis, although it can usually be made on the blood picture. Two cases of this type have been investigated, and both showed a highly cellular marrow differing in no way from that of the truly leukaemic cases.

Acute leukaemic myelosis. No case of acute myelosis with a peripheral leucocyte count of more than 15,000 per c.mm. has been included in this series. The reason for this omission is that when the peripheral blood contains many thousands of cells per c.mm. it is impossible to be certain that the puncture films represent marrow and not blood. Puncture films show no significant difference from those of the peripheral blood.

Leukopenic myelosis is a condition which is now recognized with greater frequency than in the past. Its diagnosis from examination of the blood is not always easy as the leucocyte count may be as low as 1,000 per c.mm., and myeloblasts may constitute only 5 to 10 per cent. of this total. It is commonly stated that cases occur without the presence of immature cells in the blood; no example of this type has been seen, but in Case 13/8 myeloblasts formed only 10 per cent. of a total of 1,200 leucocytes per c.mm.

Klima (1938) has described three types of sternal puncture picture in leukopenic myelosis; in the first the cellularity is greatly increased and about 90 per cent. of the cells are typical myeloblasts, paramyeloblasts, or occasionally undifferentiated cells with forms transitional to the myeloblast; secondly, the cellularity may be reduced, but the differential count similar to the first type, and thirdly the cellularity may be increased, but the differential count shows a preponderance of myeloid cells with a varying degree of shift to the left. Other authors stress the myeloblastic marrow as characteristic (Reich, 1934; Segerdahl, 1935; Schulten, 1937; Mettier and Purviance, 1937; Tischendorf, 1938*a*). Rohr (1937) and Waitz and Hoerner (1938) have reported cases in which reticulum cell hyperplasia has accompanied the marrow myeloblastosis, the former author stating that numerous lymphoid reticulum cells are common. A patchy distribution of the hyperplasia has been noted by Schulten (1937) and others, and this has induced Henning (1936) to regard the myeloblastic marrow and panmyelophthisis as variations of the same process.

TABLE

Peripheral Blood and Sternal Puncture Counts

(Cellularity: 0 = diminished, 1 = normal, 2 = increased.)

| Case. | 1/9 | | 3/2 | | 6/6 | | 12/8 | |
|----------------|--------|--------|--------|--------|--------|--------|--------|--------|
| | St. P. | Blood. | St. P. | Blood. | St. P. | Blood. | St. P. | Blood. |
| | 2 | 7,100 | 2 | 3,700 | 2 | 3,800 | 2 | 14,000 |
| Cellularity | — | — | — | — | — | — | — | — |
| Reticulum cell | 0.4 | — | — | — | — | — | — | — |
| Myeloblast | 2.8 | 10.4 | 46.4 | 25.5 | 75.0 | 74.0 | 97.8 | 96.0 |
| Promyelocyte | 4.4 | 28.8 | 8.8 | — | — | — | 0.6 | 0.4 |
| Neutrophil | — | — | — | — | — | — | — | — |
| Myelocyte | 2.8 | 0.8 | 1.0 | — | 1.0 | — | 0.2 | — |
| Young form | 1.2 | 1.6 | 0.6 | 0.5 | — | — | — | — |
| Band form | 1.6 | 3.2 | 1.6 | 2.5 | 2.0 | 3.0 | 0.2 | 0.4 |
| Segmented | 0.4 | 8.0 | 6.4 | 12.5 | — | 9.0 | 0.4 | — |
| Eosinophil | — | — | — | — | — | — | — | — |
| Myelocyte | 1.2 | — | — | — | — | — | — | — |
| Segmented | — | — | — | — | — | — | — | — |
| Basophil | 0.4 | — | — | — | — | — | — | — |
| Lymphocyte | 0.4 | 26.4 | 6.4 | 54.5 | 1.0 | 28.0 | 0.2 | 3.2 |
| Plasma cell | — | — | — | — | — | — | — | — |
| Monocyte | — | 0.8 | — | 4.5 | — | 2.0 | — | — |
| Pronormoblast | 4.8 | 0.8 | — | — | — | — | — | — |
| Normoblast | — | — | — | — | — | — | — | — |
| Basophilic | 52.4 | 6.4 | 3.2 | — | 1.5 | — | — | — |
| Polychromatic | 22.4 | 12.0 | 12.8 | — | 18.0 | — | 0.4 | — |
| Orthochromatic | 2.4 | 0.8 | 12.8 | — | 1.5 | — | 0.2 | — |
| Mitotic | 2.8 | — | — | — | — | — | — | — |

TABLE

| Case. | 18/8 | | 22/2 | | 23/3 | | 23/10 | |
|----------------|--------|--------|--------|--------|--------|--------|--------|--------|
| | St. P. | Blood. | St. P. | Blood. | St. P. | Blood. | St. P. | Blood. |
| | 2 | 9,100 | 2 | 5,200 | 2 | 5,200 | 2 | 1,760 |
| Cellularity | — | — | — | — | — | — | — | — |
| Reticulum cell | — | — | 0.4 | — | 0.2 | — | 1.2 | — |
| Myeloblast | 84.5 | 65.6 | 97.6 | 53.6 | 94.7 | 26.0 | 98.1 | 36.8 |
| Promyelocyte | 0.2 | — | 0.4 | 2.4 | 0.4 | 1.6 | 0.1 | 0.8 |
| Neutrophil | — | — | — | — | — | — | — | — |
| Myelocyte | 0.3 | — | 0.4 | — | 0.2 | 0.8 | 0.1 | 0.8 |
| Young form | 0.1 | — | 0.4 | — | 0.4 | 0.8 | — | — |
| Band form | 0.2 | 2.4 | — | 0.8 | 0.6 | 4.8 | — | 2.4 |
| Segmented | 0.1 | 1.2 | — | 4.8 | 0.3 | 7.2 | 0.1 | 9.6 |
| Eosinophil | — | — | — | — | — | — | — | — |
| Myelocyte | 0.2 | — | — | — | — | — | — | — |
| Segmented | — | 0.4 | — | — | — | — | — | — |
| Basophil | — | — | — | — | — | — | — | — |
| Lymphocyte | 10.1 | 26.4 | — | 34.4 | 0.1 | 57.2 | 0.1 | 40.8 |
| Plasma cell | 0.4 | — | — | — | — | — | 0.2 | 1.6 |
| Monocyte | — | — | — | 3.2 | — | 1.6 | — | 4.0 |
| Pronormoblast | — | — | — | — | — | — | — | — |
| Normoblast | — | — | — | — | — | — | — | — |
| Basophilic | 0.1 | — | — | — | 0.6 | — | — | — |
| Polychromatic | 2.8 | — | 0.8 | 0.8 | 2.2 | — | — | 0.8 |
| Orthochromatic | 1.0 | 0.4 | — | — | 0.3 | — | — | — |
| Mitotic | — | — | — | — | — | — | — | — |

VIII

from 16 Cases of Leukopenic Myelosis.

Blood stated as number of nucleated cells per c.mm.)

| 13/2 | | 13/8 | | 14/3 | | 15/4 | | Case. |
|--------|--------|--------|--------|--------|--------|--------|--------|----------------|
| St. P. | Blood. | St. P. | Blood. | St. P. | Blood. | St. P. | Blood. | |
| 2 | 8,000 | 2 | 1,200 | 2 | 4,200 | 2 | 2,400 | Cellularity |
| — | — | — | — | — | — | — | — | Reticulum cell |
| 93·5 | 56·0 | 89·2 | 10·0 | 15·2 | 12·6 | 84·0 | 54·4 | Myeloblast |
| 1·3 | 0·8 | 2·4 | — | 30·0 | — | 0·4 | — | Promyelocyte |
| — | — | — | — | — | — | — | — | Neutrophil |
| 0·4 | — | 0·2 | — | 13·2 | — | 1·6 | — | Myelocyte |
| 1·7 | — | 0·6 | — | 5·2 | 0·4 | 2·0 | 0·8 | Young form |
| 1·9 | 8·0 | 0·6 | 8·0 | 2·8 | 15·8 | 1·6 | 9·6 | Band form |
| 0·3 | 4·4 | 1·6 | 20·0 | 2·8 | 35·0 | 1·6 | 8·8 | Segmented |
| — | — | — | — | — | — | — | — | Eosinophil |
| — | — | 0·2 | — | — | — | — | — | Myelocyte |
| — | — | — | — | — | — | 0·4 | — | Segmented |
| — | — | — | — | — | — | — | — | Basophil |
| — | 30·4 | 2·6 | 54·0 | 4·4 | 28·8 | 2·8 | 25·6 | Lymphocyte |
| — | — | 1·2 | — | 4·4 | — | 1·2 | — | Plasma cell |
| — | 0·4 | — | 8·0 | — | 5·0 | — | 0·8 | Monocyte |
| — | — | — | — | — | — | — | — | Pronormoblast |
| — | — | — | — | — | — | — | — | Normoblast |
| 0·1 | — | — | — | 4·8 | — | 0·4 | — | Basophilic |
| 0·8 | — | 1·4 | — | 11·2 | 3·2 | 3·6 | — | Polychromatic |
| — | — | — | — | 2·0 | — | 0·4 | — | Orthochromatic |
| — | — | — | — | 0·4 | — | — | — | Mitotic |

VIII (continued)

[illegible]

Sixteen cases of leukopenic myelosis are included in this series; in one case the leucocyte count rose to 14,000 per c.mm., but in all prior to and at the time of sternal puncture the count was below 8,000 c.mm. The details of sternal puncture and blood counts are set out in Table VIII. In 10 cases (12/8, 13/2, 13/8, 15/4, 18/8, 22/2, 23/3, 23/10, 24/1, 24/5) the findings fall into Klima's first group, the marrow showing in all instances over 80 per cent. of myeloblasts. It is rare, as Mallarmé (1937) has insisted, to find a preponderance of typical myeloblasts; all these cases showed a high proportion of atypical cells. Such cells may offer considerable difficulty in identification; in two cases they were monocytoid paramyeloblasts, a variety noted by Naegeli (1931) and Krummel and Stodtmeister (1936 *b*), and not uncommonly the blood contains a higher proportion of these monocytoid cells than the marrow. In one case the vacuolated type of paramyeloblast was present—this usually offers no diagnostic difficulty—and in another an undifferentiated cell predominated with occasional forms transitional to the typical myeloblast. The remaining six showed varying proportions of micromyeloblasts which may be extremely hard to distinguish from lymphocytes. Similar cases of micromyeloblastic leukaemia are recorded by Roth (1937), Tischendorf (1938 *a*), and Mallarmé and Laverigne (1938). No case showed the increase in lymphoid reticulum cells described by Rohr (1937), but these elements must also be difficult to distinguish from micromyeloblasts.

In five cases (3/2, 6/6, 14/3, 25/7, 26/1), all of which ran a relatively prolonged course, the bone-marrow findings were of Klima's third type; some of these cases showed a number of erythroblasts, and in most cases granulopoiesis was dominated by promyelocytes and myelocytes. The final case (1/9) is of interest as it is an example of a rare condition in which progressive hyperplasia affects both leukoblastic and erythroblastic tissues. Two cases of this type have been studied; in one there were some 50,000 myeloblasts and 20,000 erythroblasts per c.mm. in the circulating blood, but for the reasons given above sternal puncture was not done. The second had 7,100 nucleated cells per c.mm. of blood, 20 per cent. of which were erythroblasts; sternal puncture films were highly cellular and contained 84 per cent. of erythroblasts. These cases of acute erythromyelosis are intermediate between myelosis proper and the acute erythrosis of di Guglielmo (1926).

Rohr (1937) has said that leukopenic myelosis is 'eine Hauptdomäne der Knochenmarksdiagnostik'; diagnosis, in fact, may be impossible without examination of the bone marrow, and in several of the present cases was not made before sternal puncture. Klima and Seyfried (1937 *a b*), Ahlberg and Nordenson (1938), and Mallarmé and Laverigne (1938) report cases of this disease where the preliminary diagnoses varied from agranulocytosis and thrombocytopenic purpura to aplastic anaemia and haemolytic anaemia; the true nature of the complaint was revealed by sternal puncture, and in some cases no myeloblasts were found in the blood.

Whether a myeloblastic marrow necessitates a diagnosis of myelosis has been questioned; it is the experience of most authors that it does, but the

possibility of myeloblastosis of the marrow in occasional cases of leukaemoid reaction remains. Klima (1938) in a large series finds no evidence of myeloblastic response to infection, but Stodtmeister (1936) has reported the case of a child with anaemia and a leukopenia of 750 per c.mm. whose sternal puncture showed 65 per cent. of myeloblasts; four months later the anaemia had been almost repaired and the sternal puncture findings were normal. This case affords a leukopenic parallel to the example of 'recovery from myeloblastic leukosis' reported by Gloor (1930). Krummel and Stodtmeister (1936 *a*) record a case with the clinical and haematological findings of leukopenic myelosis in which *Bact. paratyphosum B* was recovered from the spleen *post mortem*; there seems no reason why this should not be a secondary paratyphoid infection rather than a leukaemoid response as they claim. No cases corresponding to Klima's second type were examined.

Eosinophil myelosis. Two cases of eosinophil myelosis have been submitted to sternal puncture. The first of these was an acute case similar to those reported by Forkner, Teng, Ch'u, and Cochran (1937); it is the seventh recorded example of this disease. The peripheral leucocytes numbered 129,000 per c.mm., of which 31.6 per cent. were myeloblasts and 32.0 per cent. eosinophils of varying grades of maturity; sternal puncture films were of high cellularity with 44.8 per cent. myeloblasts and 34.8 per cent. eosinophils. The second case was one of chronic eosinophil myelosis of the type recorded by Harrison (1930) and Bass (1931). The peripheral blood contained 40,000 leucocytes per c.mm., 90 per cent. of which were eosinophils; sternal puncture films were highly cellular with 10 per cent. myeloblasts and 75 per cent. eosinophils, all but 16 per cent. of which were segmented.

2. *Lymphoid leukosis.* Not long after Virchow's (1853) separation of the two main varieties of leukosis it was recognized that bone-marrow changes often accompanied the lymphoid form as well as the myeloid (Neumann, 1870; Heuck, 1879). That this change was not invariable was shown by Leube and Fleischer (1881), when they found that the femoral marrow, in a gangrenous leg amputated from a patient with lymphoid leukosis, was of normal cellular composition. In 1904 Banti published a paper which clarified the bone-marrow changes in this condition. He described four stages in the disease process; in the first the marrow was hyperaemic, in the second it showed a simple hyperplasia of the haemopoietic elements normally present, in the third there were focal collections of lymphocytes, and in the fourth a diffuse lymphocytic metaplasia. He considered that the longer the duration of the disease the more advanced were these changes.

Various clinical and haematological types of lymphoid leukosis are encountered; in some examination of the bone marrow as a diagnostic measure is superfluous, in others it is essential. Leukaemic, subleukaemic, and leukopenic forms occur, any of which may be associated with aberrations from the classical morbid anatomical picture. The varieties may be classified as follows:

(1) The common type with generalized lymph-node enlargement and splenomegaly.

(2) The type with local tumour formation (Sternberg, 1905; Flashman and Leopold, 1929).

(3) The splenomegalic type without lymph-node enlargement (Morel, Tapic, and Bounhoure, 1925; Arneth, 1931).

(4) The medullary type without splenomegaly or lymph-node enlargement (Hess and Isaac, 1921; Rössle, 1929; Livingstone, 1932; Zanaty, 1934 *a*).

(5) The cutaneous type.

It is in the last four types, especially when associated with a subleukaemic or leukopenic blood picture, that sternal puncture is of assistance in diagnosis. I subscribe to Naegeli's (1931) view that a lymphoblastic leukaemia analogous to the myeloblastic form does not occur. I have seen cases of acute lymphoid leukaemia, but they are rare, and the predominant cell has always been the lymphocyte.³

Numerous reports of the bone-marrow findings in lymphoid leukaemia have been published. Tibial punctures are recorded by Barberi (1927) and Spuler and Schittenhelm (1913). There is general agreement that in cases with a marked peripheral lymphocytosis (over 50,000 per c.mm.) sternal puncture films show over 90 per cent. of lymphocytes (Holmes and Broun, 1933; Rohr, 1937; Willi, 1936; Nordenson, 1935; Segerdahl, 1935; Klima, 1938). As Segerdahl has pointed out, it is impossible to tell in such cases whether the puncture fluid consists of blood or marrow. In subleukaemic cases (10,000 to 20,000 lymphocytes per c.mm.) the sternal fluid usually shows a lymphocytosis of 30 to 50 per cent. (Roversi and Tanturri, 1935; Rohr, 1937; Klima, 1938). In leukopenic cases marrow lymphocytosis may be slight or absent (Weiner and Kaznelson, 1926; Klima, 1938). Henning (1938) contests these conclusions and claims that the absence of marrow lymphocytosis 'almost' negatives a diagnosis of lymphoid leukaemia. Lymphoid metaplasia has been found to persist after radiotherapy (Escudero and Varela, 1932).

In the present series 13 cases of lymphoid leukaemia are included; all were chronic, and in all but one (22/3) the blood picture was subleukaemic or leukopenic. The details are set out in Table IX. These cases confirm the observations of Rohr (1937) and Klima (1938). The only case with frank leukaemia (22/3) showed highly cellular puncture films with 97.1 per cent. of lymphoid cells; of the remainder, eight showed highly cellular marrows with over 80 per cent. of lymphocytes, the others showed lower percentages. Case 12/9 is of interest as the diagnosis had been made twelve years before when the blood count was over 100,000 leucocytes per c.mm.; repeated courses of radiotherapy had apparently rendered the sternal marrow less cellular than normal, and even after twelve years there was no increase in marrow lymphocytes. The patient subsequently died of pneumonia, and a post-mortem examination proved that he had lymphoid leukaemia.

A review of the present cases and the published reports suggests that sternal puncture may be a useful measure in the diagnosis of subleukaemic and leuco-

³ Since writing this passage I have seen a case of acute leukaemic leukaemia in which the predominant cell was a lymphoblast.

penic lymphoid leukosis. The findings of over 40 per cent. of lymphocytes in the marrow suffices for a positive diagnosis, but a normal count does not exclude the condition. Kingery, Osgood, and Illge (1937) have found the diagnosis of the cutaneous form aided by this method, and Storti (1937 *a*) and Klima and Seyfried (1937 *c*) have reported cases masquerading as thrombocytopenic purpura, aplastic and haemolytic anaemia in which sternal puncture has revealed lymphoid leukosis.

TABLE IX

| Case. | Total leucocytes per c.mm. peripheral blood. | % lymphoid cells peripheral blood. | % lymphoid cells sternal puncture. |
|-------|---|---------------------------------------|---------------------------------------|
| 1/6 | 9,600 | 98.4 | 97.1 |
| 10/4 | 7,600 | 86.0 | 95.8 |
| 11/6 | 8,300 | 63.2 | 46.0 |
| 12/9 | 5,200 | 35.0 | 10.8 |
| 13/3 | 8,000 | 76.8 | 96.0 |
| 14/1 | 11,400 | 87.2 | 88.0 |
| 19/10 | 12,000 | 60.0 | 81.8 |
| 20/7 | 14,800 | 65.3 | 45.0 |
| 22/3 | 40,000 | 98.4 | 97.1 |
| 23/2 | 9,200 | 84.0 | 12.4 |
| 23/9 | 10,400 | 58.4 | 7.2 |
| 25/2 | 8,000 | 74.2 | 83.4 |
| 25/3 | 7,200 | 55.2 | 40.0 |

3. *Monocytic leukosis*. No reports of sternal puncture in this condition have been found. In the present series one case has been studied. The blood picture was frankly leukaemic with 78,000 leucocytes per c.mm., 62.6 per cent. of which were monoblasts and 12.8 per cent. monocytes. The sternal marrow was highly cellular, and the differential count showed 83.3 per cent. monoblasts and 4.8 per cent. monocytes. Many of the monoblasts contained Auer bodies.

Myelosclerosis

This is an uncommon condition where sclerosis of the marrow cavity is associated with myeloid metaplasia in the liver and spleen, and a leuko-erythroblastic blood picture. It has been considered a form of myelosis (Hickling, 1937), but this seems improbable. Three cases have been submitted to sternal puncture; in one repeated attempts withdrew no fluid, and in each of the others only a small drop was obtained. The films were poor in cellularity and showed no significant difference from the blood; thus puncture is helpful in distinguishing this condition from chronic subleukaemic myelosis.

Erythrosis (Polycythaemia Rubra Vera of Vaquez and Osler)

The hyperplasia of the marrow which occurs in this condition has been recognized for many years from post-mortem observations (Zadek, 1927). Gibson (1908) showed that the marrow in life was markedly hyperaemic, and perhaps for this reason the changes found on sternal puncture are less remarkable than might have been anticipated. The majority of authors agree that cellularity is not greatly increased and that the erythroblast

percentage is moderately elevated (Markoff, 1936; Nordenson, 1935; Rohr, 1937; Mallarmé, 1937; Klima, 1938). In some cases the predominant erythroblasts are less mature than normal, but erythropoiesis is always orthoplastic. Megakaryocytes are often increased, but not sufficiently to have a diagnostic significance, and Nordenson (1935) has found numerous megakaryoblasts. Similar changes have been described in symptomatic erythrocytosis (Zuntz, Loewy, Müller, and Casperi, 1906; Dameshek, 1935).

Five cases of erythrosis are included in this series, and the findings are similar to those described by other authors. The erythroblast percentages varied between 30 and 45 per cent., and the maturity dispersion was normal; granulopoiesis was shifted a little to the left and megakaryocytes were not notably increased. A case of chronic erythromyelosis is described in an earlier section. These sternal puncture findings are not, of themselves, diagnostic.

Lymphadenoma Verum (Hodgkin's Disease)

Infiltration of the bone marrow occurs frequently in this disorder, but the lesions are commonly focal and not diffuse. Symmers (1924) found lymphadenomatous change in the marrow in seven of 14 cases, and Dresser's (1926) series of 95 cases contained four in which the sternum was involved. These considerations suggest that sternal puncture might at times be of diagnostic assistance. The characteristic cytology has been studied in films from punctures of lymph nodes by Hirschfeld (1925) and Schilling (1928), in imprint preparations of nodes by Fleischhacker and Klima (1936 *a*), and in films from splenic puncture by Introzzi (1932). These investigations have established the appearances possessed by the various cells of lymphadenomatous tissue in Giemsa-stained films; nevertheless it is as well to recall that no one cell is specific for this disease, and that diagnosis must depend upon the careful histological study of an excised lymph node.

Reports of sternal puncture in Hodgkin's disease have been published by several observers; of these Rohr and Hegglin (1936) and Varadi (1938) claim to have found Reed-Sternberg cells in the puncture films, but the accounts of both cases suggest that they were probably some more acute and systematized form of reticulosis than lymphadenoma verum. Klima (1938) describes as characteristic of Hodgkin's disease a cell which he considers to be a derivative of the lymphoblast. From his illustrations this cell appears to be a partly differentiated reticulum cell such as is frequently seen in imprint and puncture preparations from lymph nodes of many conditions other than Hodgkin's disease. The majority of authors find no changes beyond a shift to the left of granulopoiesis with occasional toxic changes (Tempka and Braun, 1932; Nordenson, 1935; Mallarmé, 1937; Cordier, Barbier, Croizat, and Vincent, 1937; Cordier, Croizat, Revol, and Gerbay, 1937). Barasciutti (1937) has reported six cases with 'intense eosinophilia' of the marrow, and many observers have noted aplasia after radiotherapy (Nordenson, 1935; Merwe, 1935; Klima, 1938).

The present material consists of eight cases of proven and typical Hodgkin's disease. The puncture findings depend upon the stage of the disease; in none were Reed-Sternberg cells or 'Lymphogranulomzellen' of Klima found. In three, in which the disease was well established, there were various grades of shift to the left of granulopoiesis. None of these showed a leucocytosis of over 12,000 per c.mm. In two of these cases there appeared to be some increase in megakaryocytes, a finding also reported by Young and Osgood (1935). The other cases referred to in earlier sections showed haemolytic anaemia and radiotherapeutic aplasia respectively. The changes found on sternal puncture in Hodgkin's disease are—as might have been predicted—as variable and as unspecific as the changes in the peripheral blood.

Infectious Mononucleosis

The majority of authors report no change in the sternal puncture findings beyond a moderate shift to the left of granulopoiesis (Nordenson, 1935; Rohr, 1937; Schulten, 1937; Klima, 1938; Henning, 1938). Freeman (1936) has found an increase in lymphocytes, Markoff (1936) in lymphocytes and plasma cells, and Mallarmé (1937) in lymphocytes and monocytes; it seems probable that these were due to dilution with peripheral blood. In the present series one case only has been punctured, and here the findings were within normal limits. The method has little value in diagnosing this condition, for even the finding of a normal marrow does not exclude lymphoid leukosis.

Lipoidosis

The diagnosis of Gaucher's disease has been confirmed in one or two cases by tibial puncture (Barchasch and Gurin, 1931; Löwinger, 1935a), but reports suggest that sternal puncture fluid frequently contains none of the specific cells (Pittaluga and Rof, 1932; Sokolowski, 1932). Klima (1938) and Rohr (1937) have obtained positive findings with sternal puncture, and the latter author distinguishes two types of cell, an immature one resembling a large lymphoid reticulum cell and a mature one of 20 to 30 μ , with a faintly granular, almost colourless cytoplasm, and a small pyknotic nucleus eccentrically placed. In one case in the present series only a drop of fluid could be aspirated, but in this an occasional cell of the mature type was found. Kato (1937) reports the recovery of the specific cells of the Niemann-Pick syndrome from sternal puncture.

Other Types of Reticulosis

Reports of bone-marrow punctures in the less common types of reticulosis are few. Arinkin (1929), Dameshek (1933), and Rohr and Hegglin (1936) have recorded cases in which atypical cells were present in sternal puncture films. In the present series eight such cases were studied; six are without interest, showing only a normal bone marrow or a slight shift to the left; a seventh had a 'secondary' agranulocytosis with necrotic angina, the leucocyte

count being 600 per c.mm., with 30 per cent. neutrophils. Sternal puncture showed a highly cellular marrow containing 19.2 per cent. promyelocytes. Another case had a most unusual blood picture with about 30 per cent. of primitive cells which were probably prohistiocytes (Scott and Robb-Smith, 1936) and histiocytes; the bone marrow showed numerous cells of this type together with occasional phagocytic cells.

Reticulosarcoma

Rohr and Hegglin (1936) have observed a case of reticulosarcoma in which the sternal puncture films contained numerous large undifferentiated cells. Excluding myelomatosis there are four cases in this series. A polymorphic-cell example (Hodgkin's sarcoma) had a normal count; a case of syncytial reticulosarcoma showed a marked erythroblastic hyperplasia with 53 per cent. of normoblasts; and in two cases of the lymphoblastic type, 14.6 per cent. and 89 per cent. of lymphocytes were present.

Myelomatosis

Hirschfeld suggested in 1925 that biopsy of the bone marrow would, on theoretical grounds, afford the best means of diagnosing myelomatosis; since that time numerous reports have proved the validity of his suggestion (Zadek and Lichtenstein, 1932; Young and Osgood, 1935; Henning, 1935; Markoff, 1936; Skouge, 1936; Schulten, 1936; Reich, 1936; Ferrata and Storti, 1937; Curtze, 1938). In all these reports sternal puncture showed a high proportion of 'myeloma cells'. Controversy has raged over the nature of the 'myeloma cell' since the histology of the disease was first described by von Rustizky (1874). Plasma-cell, lymphoblastic, myeloblastic, and erythroblastic types have been described, but, as Wallgren (1921) has pointed out, the cell type recorded as most common has varied with the changing trend of pathological thought from round cell to plasma cell and later to myeloblast. For this reason he prefers to believe that only one type really exists and since the introduction of sternal puncture, observations have tended to confirm his belief (Fleischhacker and Klima, 1936 *b*; Schulten, 1937; Rohr, 1937). Varadi (1937 *a*), Zadek (1937), and Stewart and Weber (1938) still consider that different types occur. Klima (1938) has traced the development of the 'myeloma cell' from an undifferentiated precursor which resembles the myeloblast, and he suggests that varying grades of differentiation account for the reports of different cell types. Rohr (1937) believes that the 'myeloma cell' is a pathologically altered reticulum cell, but Ross, Discombe, and Robb-Smith (1937) believe it to be a dysplastic haemocytoblast.

Whatever the nature of this cell, the great majority of sternal punctures have shown a picture of remarkable uniformity in myelomatosis. There is a varying proportion of large round or ovoid cells with a diameter of 15 to 30 μ : the nucleus has a diameter of 5 to 7 μ , is commonly eccentric,

occasionally nucleolated and leptochromatic, but more often stains densely; a cart-wheel arrangement of the nuclear chromatin is uncommon in films. The cytoplasm is basophilic and a pale perinuclear zone is seen in some cells; cytoplasmic vacuoles are frequently present. Larger forms may be found with two or three nuclei, but mitotic figures are not seen, and Russell's bodies do not occur. Staining by methods 'specific for the plasma cell', such as Pappenheim's pyronin methyl green, have given equivocal results.

Two cases of myelomatosis are included in the present series. In the first 17.2 per cent. of the cells in the puncture films were typical 'myeloma cells', and in the second 9.6 per cent. In the second case, however, 57.2 per cent. of the cells were primitive lymphoid elements from which all forms transitional to the true 'myeloma cell' could be found. This observation recalls the case of 'lymphoblastic and plasma-cell myeloma' recorded by Klemperer (1920), and both may be explained on Klima's (1938) hypothesis as partly undifferentiated. In the second case some of the puncture fluid was allowed to clot and sections cut of the material; the 'myeloma cells' in these preparations had the characteristic tinctorial features of the plasma cell. Sternal puncture thus affords a rapid and certain means of diagnosing myelomatosis, and many cases have been recorded where diagnosis would have been impossible without examination of the bone marrow.

Metastatic Neoplasms of Bone

Rohr and Hegglin (1936) in a study of 74 cases of carcinoma were able to find carcinoma cells in the sternal punctures of ten; they described a small cell commonly seen in bronchial carcinoma and a large cell in gastric and prostatic carcinoma. It is often difficult to aspirate material in osteosclerotic carcinomatosis, and only a small drop may be obtainable. Numerous authors record the discovery of neoplastic cells in sternal puncture films (Mallarmé, 1937; Klima, 1938; Henning, 1938). Varadi (1937*b*) has recorded a unique case in which costal puncture led to a diagnosis of metastatic malignant hepatoma, and Schulten (1937) suggests that puncture in such cases should be performed on the bones where radiographic changes are evident. Since there have been no demonstrable radiographic changes in the last four cases of skeletal carcinomatosis I have seen, this suggestion has only a hypothetical value. Pässler's (1931) observations on the frequency of solitary metastases in the manubrium sterni do suggest that, when carcinomatosis is suspected, puncture should be made in this site.

Two cases of skeletal carcinomatosis are included in this series; in a third repeated puncture failed to withdraw any fluid from the sternum. All three cases were confirmed *post mortem* and all had a leuko-erythroblastic blood picture (Vaughan, 1936*a*). In the first case—one of carcinoma of the prostate—only a minute drop of fluid was obtained, but in this sheets of cells of Rohr and Hegglin's small type were found. The second case gave very cellular films, showing abnormally active erythropoiesis and granulopoiesis

with a shift to the left; in addition there were clumps of large cells 10 to 20 μ in diameter with grey-blue cytoplasm and nuclei containing many nucleoli (large-cell type). These cells possessed the features described by Quensel (1928) as characteristic of carcinoma cells. Similar cells have not been found in cases other than carcinomatosis. Sternal puncture may prove of the greatest value in the diagnosis of carcinomatosis of the skeleton, especially when such cases exhibit merely a myelophthisic or leuko-erythroblastic anaemia.

Agranulocytosis

A wealth of contradictory reports have been published on the bone marrow changes in agranulocytosis. It is likely that agreement is lacking because neutropenia and a resultant liability to infection are symptoms common to many morbid processes. Of these, agranulocytosis as a result of idiosyncrasy to amidopyrin and other drugs is a well-defined condition, and Plum (1937) has shown that all the cases examined had a selective hypoplasia of the granulocytes and their precursors in the bone marrow; if puncture was made during the recovery phase an accumulation of primitive granulocytes might give the appearance of 'maturation arrest'. The majority of other writers have followed Rohr (1937) and considered all cases showing the agranulocytic syndrome together. Three main marrow changes are described; severe cases with granulopoietic aplasia, moderately severe cases with a promyelocytic marrow, and mild cases with a myelocyte young-form marrow (Nordenson, 1935; Klima, 1938).

The typical syndrome of Werner Schultz due to idiosyncrasy to amidopyrin is of great rarity in hospital practice in this country and no cases have been available for sternal puncture. Three cases showing profound neutropenia have been studied; one was the example of chronic panmyelophthisis referred to above, another the case of acute reticulosis previously described, and the third a case of chronic neutropenia of unknown cause which had a myelocyte young-form marrow. These three cases, although showing the agranulocytic syndrome, were all of different aetiology and in each case also the bone marrow was different. It is clear that many conditions give rise to agranulocytosis, but sternal puncture sometimes may be helpful in revealing an underlying cause such as leukosis or panmyelophthisis.

Idiopathic Thrombocytopenic Purpura

There is no agreement over the bone-marrow changes in this complaint. Seeliger (1924) described a lack of granulation in the megakaryocytes, and Rohr and Koller (1936) have found an increase in these elements with similar 'toxic' changes. Markoff (1938) has pointed out that quantitative estimations of megakaryocytes in sternal puncture material are not possible as the normal is so variable; she finds no changes in maturity dispersion of the series and holds that the 'toxic' changes are merely a part of normal

maturation of the cell. Only one case has been investigated, and in this megakaryocytes were certainly more abundant than in most films, but the changes noted by Rohr (1937) were not striking.

Sternal Puncture in Infection

The changes in the bone marrow in infection have been studied by a number of workers, notably Bantz (1922), Yamamoto (1925), Schilling (1925), and Barta (1933). Schilling distinguishes six different marrow pictures, the predominant cell becoming less mature throughout the series; the findings of other writers are similar. The changes have no diagnostic significance and cannot be discussed at length, but a prognostic value has been claimed for them. The published papers give the impression that the separation into numerous types is artificial and that it is more helpful to picture a shift to the left of granulopoiesis going *pari passu* with the severity of the infection. In infections associated with neutropenia (typhoid fever—Storti and Filippi, 1937; Galinowski, 1938; influenza—Schnetz and Greif, 1937, 1938), the findings are commonly a marrow poor in cells with a lack of mature granulocytes; in accordance with popular haematological doctrine this has been interpreted as a 'maturation arrest'.

A few cases with infections have been investigated, and the changes consist of an increase in granulopoietic cells with a varying degree of shift to the left; the immaturity varies with the stage of the infection and with the severity of the toxæmia, but no prognostic value could be attached to the findings in the few cases studied.

Sternal Puncture in Tropical Infections

Seyfarth (1923) originally introduced sternal trephining as an alternative to splenic puncture for the diagnosis of kala-azar and malaria. Kassirsky (1932) has found parasites in the bone marrow in these two conditions and in relapsing fever; in the last disease they were absent from the blood. Later reports of its value in the diagnosis of malaria have been contradictory (Voorhoeve, 1937; Lebon, Manceaux, Fabregoule, and Fanjeaux, 1937). No opportunity for sternal puncture in cases of malaria has arisen, and in one case of kala-azar no parasites could be found; but by the courtesy of Dr. J. H. Hunt films showing Leishman-Donovan bodies in phagocytic cells from sternal puncture have been examined. Guerschénovitch and Titoff (1934) have found the method valuable in the diagnosis of infantile kala-azar.

Summary

1. The technique of sternal puncture is described and an account is given of the findings in normal and diseased subjects.
2. Sternal puncture has provided the haematologist with a new diagnostic weapon and in doing so has moved the focus of interest from the peripheral blood to the bone marrow. It has already clarified many points in the

pathology of disordered haemopoiesis, and since Rohr and Hafter (1937) have shown that changes occur in the marrow with great rapidity after death, examination *in vivo* must now take precedence over post-mortem studies.

3. The value of the method is shown by the ease and certainty with which anaemias due to deficiency of liver complex may be recognized; it offers the only certain means of diagnosis in many cases of subleukaemic and leukopenic leukosis and of myelomatosis, and it has proved useful in the recognition of kala-azar and relapsing fever.

4. Finally, sternal puncture provides an opportunity of haemocytological education which has never previously existed; it is, in Schulten's (1937) words 'die Hochschule für den Hämatologen'.

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DESCRIPTION OF COLOURED PLATE

Normoblast series (1-5), from normal bone marrow.

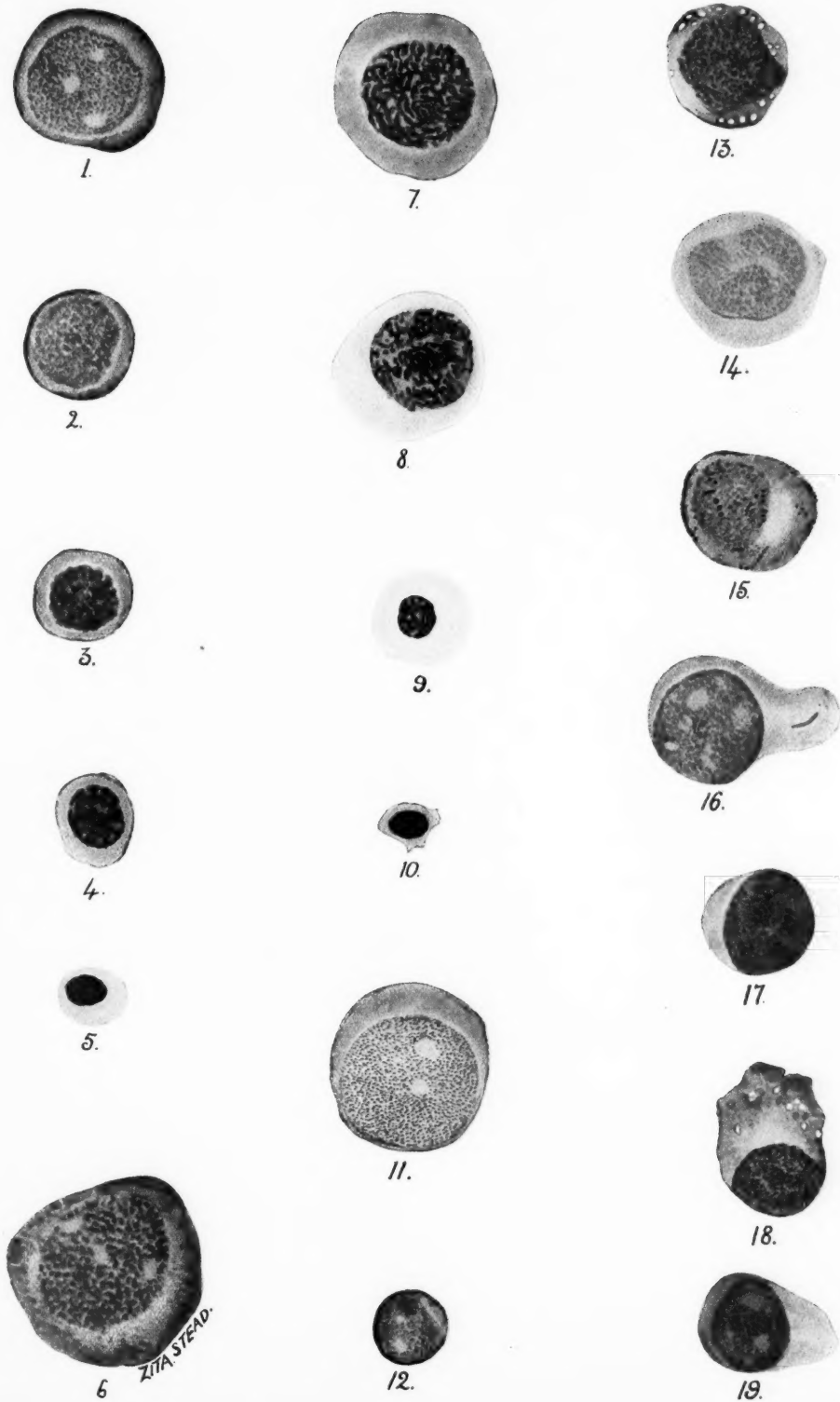
1. *Pronormoblast*. (Diameter 19μ ; diameter of nucleus 14.5μ .) The cytoplasm is deeply basophilic with a paler perinuclear halo; the nucleus is of a fine stippled texture and contains three nucleoli.
2. *Basophilic normoblast*. (Diameter 14μ ; diameter of nucleus 10μ .) The cytoplasmic basophilia is less intense than in the pronormoblast and the nuclear pattern is coarser. The nucleus is becoming basichromatic and nucleoli have disappeared.
3. *Basophilic normoblast*. (Diameter 10.5μ ; diameter of nucleus 9μ .) The changes have progressed farther than in the previous cell.
4. *Polychromatic normoblast*. (Diameter 10μ ; diameter of nucleus 7μ .) The cytoplasm has become slate-grey and the nuclear chromatin is arranged in coarse clumps.
5. *Orthochromatic normoblast*. (Diameter 7.5μ ; diameter of nucleus 4.5μ .) The cytoplasm is now orthochromatic, but still a little less acidophilic than in the mature erythrocyte; all trace of structure in the nucleus has vanished and it is now densely basichromatic.

Megaloblast series (6-9), from the bone marrow in pernicious anaemia.

6. *Promegaloblast*. (Diameter 24μ ; diameter of nucleus 16μ .) The cytoplasm is deeply basophilic with a paler perinuclear zone; the nuclear pattern is coarser than in the pronormoblast and the chromatin tends to be arranged in curved rods separated by bands of parachromatin; three nucleoli are present.
7. *Basophilic megaloblast*. (Diameter 20μ ; diameter of nucleus 14μ .) The cytoplasmic basophilia is less intense than in the previous cell and the perinuclear halo is less definite. The nucleus appears sharply defined and the nuclear chromatin has undergone aggregation into coarser rods with well-marked intervening spaces of parachromatin; the nucleoli have disappeared.
8. *Polychromatic megaloblast*. (Diameter 15.5μ ; diameter of nucleus 12μ .) The basophilia of the cytoplasm has been replaced by a uniform pale-grey polychromasia. The coarse reticular pattern of the nucleus has been maintained, but the nucleoplasm is more basichromatic and in places is formed into clumps.
9. *Orthochromatic megaloblast*. (Diameter 10μ ; diameter of nucleus 5μ .) The cytoplasm shows the same degree of eosinophilia as a mature erythrocyte; the nucleus is eccentric and its coarsely clumped basichromatin still shows the traces of a pattern. The cytoplasmic eosinophilia is more intense and the nuclear pyknosis less than in the homologous normoblastic cell.
10. *Polychromatic normoblast from bone marrow in iron-deficiency anaemia*. (Diameter 8μ ; diameter of nucleus 4.5μ .) The cell outline is irregular and ragged, the cytoplasm shows a deep grey polychromasia and the nucleus is densely pyknotic. This cell differs from the healthy polychromatic normoblast in being smaller, irregular in outline, having a greater degree of cytoplasmic polychromasia and of nuclear pyknosis.

Myeloblasts (11-14).

11. 'Classical' *myeloblast from normal bone marrow*. (Diameter 20μ ; diameter of nucleus 17.5μ .) The cytoplasm is basophilic with a deeply staining rim fading as the perinuclear zone is approached. The eccentric nucleus which stains palely and contains two nucleoli presents a finely stippled pattern with a little condensation of chromatin at its edge and around the margin of the nucleoli.
12. *Micromyeloblast from the bone marrow of a case of leukopenic myelosis*. (Diameter 10μ .) The nucleus stains more deeply than in the previous cell, its pattern is coarser and it occupies almost the whole cell body, revealing only a small area of basophilic cytoplasm with a deeply staining rim.
13. *Vacuolated paramyeloblast from the bone marrow of a case of leukopenic myelosis*. (Diameter 15μ ; diameter of nucleus 10μ .) The cytoplasm is slightly basophilic and contains numerous colourless vacuoles; the arrangement of the nuclear chromatin is less fine than in the classical myeloblast.
14. *Monocytoid paramyeloblast from the bone marrow of a case of leukopenic myelosis*. (Diameter 20μ ; diameter of nucleus 15μ .) The cytoplasm stains a homogeneous pale grey-blue; the nucleus has a pale stippled pattern.
15. *Promyelocyte from normal bone marrow*. (Diameter 15μ ; diameter of nucleus 10μ .) The nucleus retains most of the characteristics of that of the classical myeloblast, but the chromatin has undergone a little condensation to produce a less fine stippling and the nucleoli have disappeared. The basophilia of the cytoplasm is less intense and scattered through the cell are coarse violet granules.
16. *Monoblast from the bone marrow of a case of monocytic leukaemia*. (Diameter 21.5μ ; diameter of nucleus 14.5μ .) The grey-blue cytoplasm is drawn out to form a pseudopodium and contains an intensely eosinophilic rod-like 'Auer body'. The nuclear pattern is for the most part stippled, but in places a suggestion of a skein-like arrangement can be seen.
17. *Lymphoblast from the bone marrow of a case of lymphoid leukaemia*. (Diameter 14.5μ ; diameter of nucleus 12.5μ .) The cytoplasm is basophilic with a paler perinuclear halo; the nucleus is more basichromatic and has a coarser texture than in the classical myeloblast.
18. *Myeloma cell from the bone marrow of a case of myelomatosis*. An elongated cell measuring about $18\mu \times 12\mu$; diameter of nucleus 10μ . The nucleus is at one extremity of the cell; the nuclear chromatin is disposed in fine clumps; no nucleoli are present. The cytoplasm stains blue-mauve and contains a number of colourless vacuoles.
19. *Carcinoma cell from the bone marrow of a case of diffuse skeletal carcinomatosis*. An ovoid cell measuring about $19\mu \times 12\mu$; diameter of nucleus 10μ . The nucleus is situated at one end of the cell and is of coarse texture, slightly basichromatic and contains several large nucleoli which stain violet. The cytoplasm is grey in colour and has a 'ground-glass' appearance.



Magnification $\times 1300$. All cells stained by May-Grünwald-Giemsa method

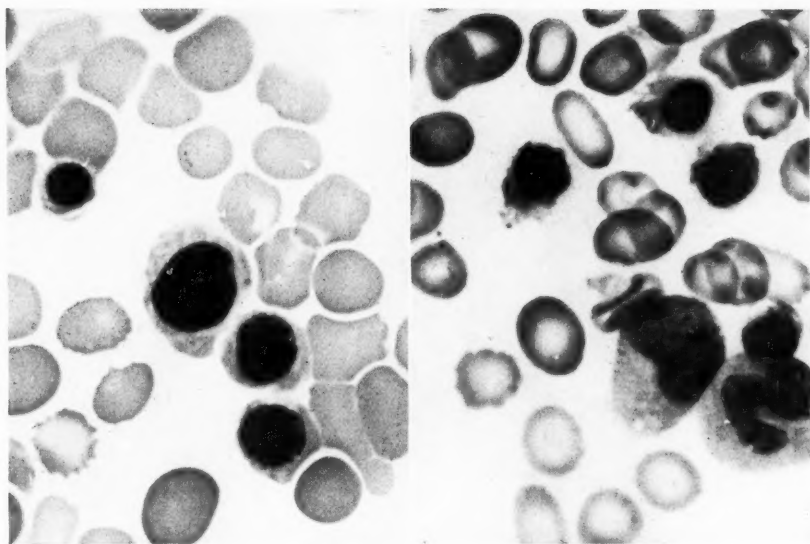


FIG. 4. Polychromatic normoblasts from films of normal sternal puncture (left) and iron-deficiency anaemia (right) showing irregular cell outline and pyknotic nucleus in the latter ($\times 1350$)

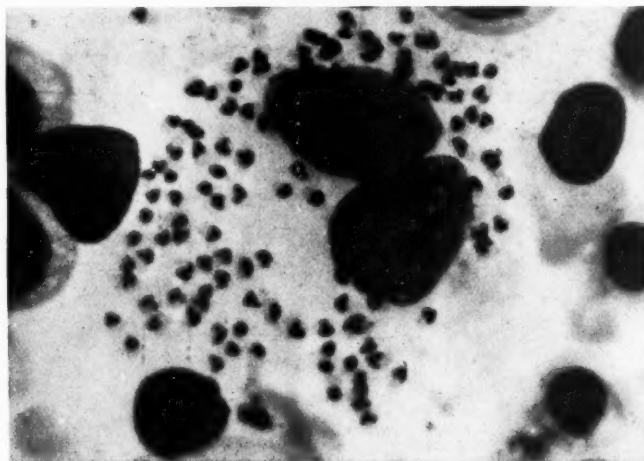


FIG. 5. Phagocytic cell containing Leishman-Donovan bodies in sternal puncture film from a case of kala-azar ($\times 1600$)

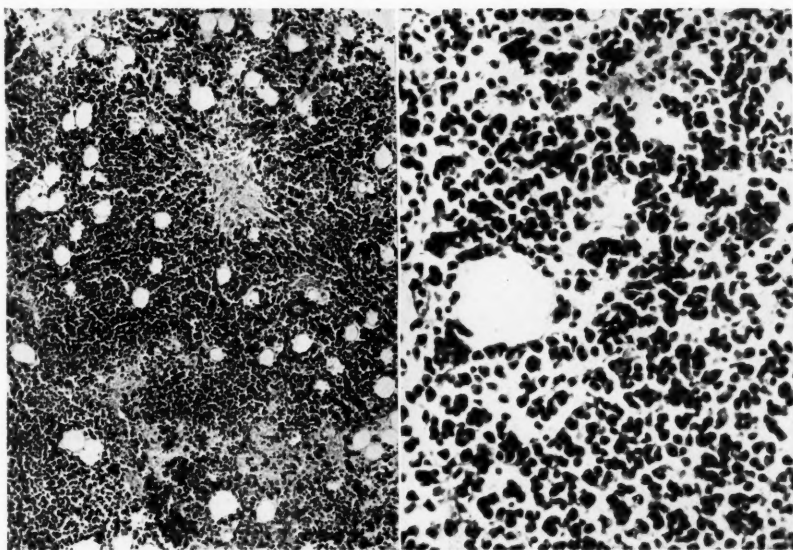


FIG. 6. Photomicrographs of sections of fragments in sternal puncture material from a case of myelomatosis (left $\times 105$; right $\times 325$)

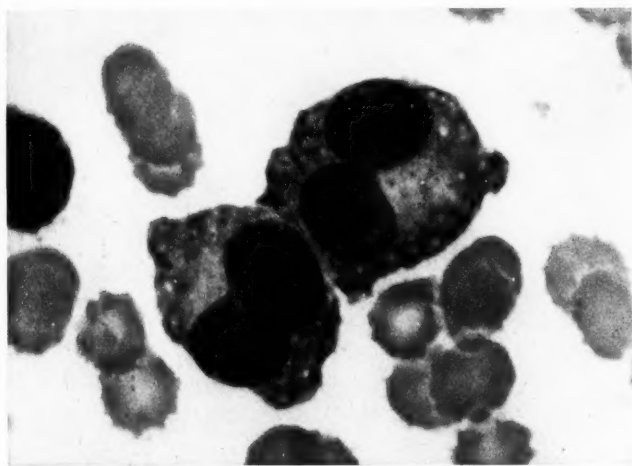


FIG. 7. Myeloma cells in films from sternal puncture from a case of myelomatosis ($\times 1600$)

THE AGGLUTINATION OF SUSPENSIONS OF VIRUS-LIKE PARTICLES PREPARED FROM EXUDATES IN ACUTE RHEUMATIC FEVER¹

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Introduction

THE contribution of Schlesinger, Signy, Amies, and Barnard (1935) to the aetiology of acute rheumatic fever has resulted in renewed interest not only in the virus theory itself but also in its bearing upon other causative factors, singly or in combination with it. The essentials of their conclusions may be briefly summarized in view of more recent studies along similar lines. They assumed that if a virus was responsible for the most active and extensive inflammatory lesions of acute rheumatic fever, high-speed centrifugalization of pericardial exudates might result in the deposition of particles resembling the elementary bodies of recognized virus material. They then found that suspensions of such particles could be obtained from pericardial exudates, and in one instance, from a pleural effusion, and that these were specifically agglutinated by the sera of patients suffering from and resisting successfully an acute rheumatic infection. Sera from quiescent cases did not, as a rule, agglutinate the suspensions, which favoured the view that the reaction was in the nature of an antibody response to an acute specific infective process. This view was further strengthened by the observation that a control group of sera, including nine cases of syphilis, four cases of active Still's disease, two cases of active rheumatoid arthritis, 12 cases of herpes zoster, and two cases of recent streptococcal tonsillitis, did not agglutinate rheumatic suspensions. Nor were suspensions from non-rheumatic materials agglutinated by any of the test or control sera. By comparison with serological data in known virus infections the evidence was sufficiently strong to lead to the conclusion that these exudates contained a virus responsible for a share, at least, in the production of acute rheumatic infection.

The strikingly specific quality of the agglutination reaction for acute rheumatic fever was surprising in view of considerable evidence which has accumulated from clinical observation and scientific investigation in favour of a close relationship and overlapping among the chief members of the rheumatic group of diseases, i.e. acute rheumatic fever, acute rheumatoid arthritis, and acute chorea. When a larger and more comprehensive group of cases was studied by Eagles, Evans, Fisher, and Keith (1937) it was

¹ Received February 6, 1939.

found that agglutination was not confined to acute rheumatic fever, though it occurred with sufficient regularity to confirm such an inter-relationship when selected and typical cases were investigated. Generally speaking, about half the sera tested gave agglutination, and cross-agglutination tests pointed to some common antigenic factor. A control group of 21 cases selected on the basis of a completely negative history of any rheumatic manifestation gave no agglutination. Concurrently, the infectivity of these suspensions which had been satisfactorily agglutinated was tested in monkeys. No evidence of infection definitely attributable to the suspensions could be demonstrated by these workers (1938). A further series of transmission experiments, using other animals, has been equally unsuccessful (Schlesinger and Signy, 1938).

There exists a large group of clinical cases which do not conform to recognized classifications of true rheumatism, and by virtue of joint manifestations are conveniently styled 'arthropathies'. In some instances bacterial infection can be demonstrated in the joint itself, as in tuberculous or gonococcal infection; in others the joints appear to be involved non-specifically as part of a reaction to a focus elsewhere; and in still others no cause can be found. It was decided to investigate the ability of sera from cases in this group of arthropathies to agglutinate rheumatic suspensions in place of the control group which bore no possible relation to rheumatism.

Eagles, Evans, Fisher, and Keith (1937) had failed to correlate agglutination with any precise phase in the clinical history of rheumatic patients. It was decided, therefore, to study a fresh series of these cases under prolonged clinical observation, paying particular attention to streptococcal infection and its various manifestations, in the hope that some light might be thrown upon the nature of the agglutination phenomenon and the conditions governing it.

Clinical Material

It was fully recognized that the results of a combined clinical and laboratory investigation in rheumatism, in which present classifications lack sharp definition, ultimately depend to a great extent on personal clinical judgement for the eventual placing of cases in the groups about to be discussed. The clinical side was undertaken by W. H. B., who is solely responsible for it. It must, however, be recorded that the final diagnosis was arrived at frequently after two or three opinions by the Honorary Physicians in charge of the cases. Obscure clinical states were fully discussed by Professor J. A. Ryle and the staff of the Department of Medicine of the University of Cambridge. It is, therefore, reasonably safe to assume correct diagnoses in view of the fact that in the end no difficulty was met in casting the cases into the three main clinical groups considered. This grouping is based upon that adopted by the Nomenclature Sub-committee of the National Committee on Chronic Rheumatic Diseases (1935). The cases

studied were 54 consecutive patients admitted to the medical wards of Addenbrooke's Hospital, Cambridge, during 1937 and 1938, in whom joint pain was a presenting feature. There was otherwise no intentional selection.

Group I. Rheumatic fever (18 cases).

Cases of obvious juvenile rheumatism with carditis, or chorea, or both. One adult (F. L., male, aged 43 years), in whom at *post mortem* unquestionable macroscopic and microscopic evidence of rheumatic fever was present, is included.

Group II. Arthritis of rheumatoid type of 'unknown aetiology' (20 cases).

(a) Cases of metastatic or 'focal' arthritis, including the so-called 'multiple infective arthritis'.

(b) Climacteric arthritis (villous type).

(c) Classical type of rheumatoid arthritis in women, usually in the child-bearing epoch.

(d) Rheumatoid arthritis in children, including Still's disease.

Group III. Other arthropathies (16 cases).

Cases which could not be included in Groups I and II.

(a) Arthritis of rheumatoid type of known aetiology, i.e. gonococcal and pneumococcal arthritis.

(b) Gout.

(c) Joint disease not of the rheumatoid type.

Technical Procedure

Serum was obtained by the usual method, stored at 4° C. and used for agglutination tests as soon as possible. To avoid 'lipoid' in serum, blood was taken between 10 a.m. and the mid-day meal. Usually it was necessary to filter sera through L₂ candles, and in some instances where these precautions were ineffective samples were discarded.

Antistreptolysin determinations (by W. H. B.). The antigen used, reduced (O₂ labile) streptolysin (S.O.), was prepared by Dr. E. W. Todd and generously supplied by the London County Council. Titrations were standardized against antistreptolysin O (A.S.O.) horse serum. The technique of titration was essentially that of Todd (1932, 1938), the A.S.O. being determined by the greatest dilution of serum sufficient completely to protect washed rabbit red blood-cells against haemolysis by 1 unit of streptolysin O. The number of antistreptolysin units recorded is the reciprocal of this dilution.

Agglutination of rheumatic suspensions (by G. H. E.). The technical procedure was essentially that described earlier (Eagles, Evans, Fisher, and Keith, 1937). Suspensions were prepared only from rheumatic exudates (pericardial and pleural), and every effort was made to ensure that these were from cases in which the exudate was a manifestation of active, acute rheumatic pericarditis and pleurisy. Pleural exudates were aspirated during life, as were also a certain proportion of pericardial exudates. The supply of suitable exudates was never equal to the demand. Consequently pooling

TABLE I

| Column number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---|-----------|---|--------------------------------------|--------------------------------|----------------------------|----------|---|-----------------------------|--------------------|----------------|--|---|
| | Patients. | | Number of samples of serum showing:— | | | | | | | | | |
| | No. | Number showing positive E.B.A. at any time. | Number of samples examined. | Elementary body agglutination. | | | Antistreptolysin 'O' titre (Todd units) (evidence of <i>Strep. pyogenes</i> infection). | | | | Percentage of patients showing frank evidence of <i>Strep. pyogenes</i> infection. | |
| | | | | Number positive E.B.A. | Percentage positive E.B.A. | 100 none | 100-200 equivocal. | 250-312 practically certain | 500-1,000 certain. | 1,000 certain. | Immuno-logical (columns 9 + 10). | Bacterio-logical. Positive cultures on admission. |
| <i>Group 1. Rheumatic fever.</i> | | | | | | | | | | | | |
| Active polycyclic | 11 | 6 | 77 | 32 | 42 | ... | 1 | 20 | 29 | 27 | 100 | 73 |
| Monocyclic | 5 | 5 | 20 | 13 | 65 | ... | ... | 4 | 8 | 8 | 100 | 60 |
| Total active | 16 | | 97 | 45 | 46 | ... | 1 | 24 | 37 | 35 | | |
| Recovering polycyclic (Same cases) monocyclic | 6 | 1 | 19 | 2 | 11 | ... | ... | 11 | 8 | ... | ... | ... |
| | 2 | 2 | 8 | 6 | 75 | ... | ... | 3 | ... | 5 | ... | ... |
| Total recovering | 8 | | 27 | 8 | 30 | ... | ... | 14 | 8 | 5 | | |
| Inactive (same cases) | 4 | 0 | 8 | ... | 0 | ... | ... | 5 | 1 | 2 | ... | ... |
| Chorea only | 2 | 1 | 2 | 1 | 50 | ... | 1 | ... | ... | 1 | 50 | 50 |
| Total rheumatic fever | 18 | 12 | 134 | 54 | 40 | ... | 2 | 43 | 46 | 43 | 94 | 66 |
| <i>Group 2. Arthritis of rheumatoid type.</i> | | | | | | | | | | | | |
| Active | 12 | 8 | 67 | 27 | 40 | 8 | 10 | 11 | 13 | 25 | 58 | 42 |
| Quiescent (same cases) | 7 | 1 | 11 | 1 | 9 | ... | 4 | 5 | 2 | ... | ... | ... |
| Total | 12 | | 78 | 28 | 36 | 8 | 14 | 16 | 15 | 25 | | |
| Relentlessly active | 2 | 1 | 12 | 1 | 8 | ... | 2 | 1 | 1 | ... | 50 | 0 |
| Burnt out | 6 | 2 | 14 | 7 | 50 | 12 | 1 | 1 | ... | ... | 0 | 0 |
| Total rheumatoid arthritis | 20 | 11 | 104 | 36 | 35 | 28 | 17 | 18 | 16 | 25 | 40 | 25 |
| <i>Group 3.</i> | | | | | | | | | | | | |
| Other arthropathies. Total | 16 | 8 | 60 | 25 | 42 | 20 | 34 | 6 | ... | ... | 0 | 1 of 12 |
| Totals | 54 | 31 | 298 | 115 | 39 | 48 | 53 | 67 | 62 | 68 | 60 | ... |

E.B.A. = Elementary body agglutination with dilutions of sera ranging from 1 in 4 to 1 in 64.

TABLE II

| Group 3. | Other arthropathies | Case. | Number of sera examined. | Elementary body agglutination. | | Antistreptolysin 'O' titre (Todd units) (evidence of <i>Strep. pyogenes</i> infection). | | | | <i>Strep. pyogenes</i> recovered from throat on admission. | Intercurrent streptococcal infections. |
|-----------------------------------|---------------------|-------|--------------------------|--------------------------------|----|---|--------------------|------------------------------|--------------------|--|--|
| | | | | | | 100 none. | 100-200 equivocal. | 250-312 practically certain. | 500-1,000 certain. | | |
| Acute infections with joint aches | | RB | 1 | 1 | — | — | 1 | — | — | No | Type 6 in hospital |
| | | KD | 6 | 6 | — | 3 | — | 3 | — | No | |
| Gout | | WT | 2 | 1 | 1 | — | 2 | — | — | No | |
| Suppurative arthritis. | | BB | 1 | — | 1 | — | 1 | — | — | — | |
| Pus sterile | | HB | 2 | — | 2 | 2 | — | — | — | No | |
| Pneumococcal | | WB | 12 | 5 | 7 | — | 11 | 1 | — | A few un-typed | |
| Pus not examined | | | | | | | | | | | |
| Gonococcal arthritis | | RB | 10 | 3 | 7 | 10 | — | — | — | No | No evidence |
| Ankylosing spondylitis | | TH | 2 | — | 2 | — | — | — | — | No | |
| Miliary tuberculosis— | | OL | 3 | — | 3 | — | 3 | — | — | No | |
| joint pains | | MD | 4 | 3 | 1 | — | 4 | — | — | No | |
| Anorexia nervosa. | | GF | 4 | 4 | — | — | 4 | — | — | No | |
| Decubitus deformities | | EG | 1 | — | 1 | 1 | — | — | — | No | |
| Periarteritis nodosa | | JH | 4 | — | 4 | 3 | 1 | — | — | — | |
| Effort syndrome— | | DP | 2 | — | 2 | — | 2 | — | — | No | |
| joint aches | | | | | | | | | | | |
| Subacute bacterial | | | | | | | | | | | |
| endocarditis. Con- | | JT | 5 | 2 | 3 | — | 3 | 2 | — | No | Type 3 in hospital |
| genital heart disease | | AS | 1 | — | 1 | 1 | — | — | — | — | |
| Osteoarthritis | | | 60 | 25 | 35 | 20 | 34 | 6 | — | 1 of 12 | |
| Total (16 patients) | | | | | | | | | | | |

Elementary body agglutination observed in 8 of 16 patients. *Streptococcus pyogenes* may have been of aetiological importance in one case only.

of suspensions was, for the most part, essential. Fractional centrifugalization, other than to yield an even dispersion of the particles, was not practical in many instances and was not carried out. Suspensions from pathological exudates other than acute rheumatism were not tested, since these had already been investigated and were not an essential feature of the present work.

Results

In Table I is set out a summary of agglutination of rheumatic suspensions by sera tested at frequent intervals during the clinical course of the three groups under investigation. The incidence of *Streptococcus pyogenes* infection is indicated, with an analysis of the resultant antistreptolysin O titres.

The occurrence of agglutination with a large number of sera from patients in the third group (other arthropathies) is especially interesting. The data for this group is, therefore, set out in Table II, which includes a list of the clinical states investigated.

Agglutination of rheumatic suspensions was not confined to sera from rheumatic fever and rheumatoid arthritis, but occurred with sera from cases of other arthropathies in which any relationship to true rheumatism was remote. It will be seen from the following figures that in the three groups there is no significant difference in the occurrence of agglutination :

| | No. of patients. | No. of samples of serum. | Positive agglutinations. |
|----------------------------|------------------|--------------------------|--------------------------|
| Group I. Rheumatic fever | 18 | 134 | 40 per cent. |
| " II. Rheumatoid arthritis | 20 | 104 | 35 " |
| " III. Other arthropathies | 16 | 60 | 42 " |

It is unlikely that the occurrence of agglutination in the three groups is haphazard, since an analysis of full details shows a definite tendency for it to occur in some cases with much greater frequency than in others. Moreover, when a number of positive agglutinations was obtained with sera from the same patient taken at different times, it was usual for these to be grouped together in a sequence, although two such sequences might be encountered during the clinical course. Various dilutions of each serum were tested with the suspension. It may be asked whether the titre of the sera was low in one group and high in another. The following analysis stated in percentages of dilutions more than 1 in 4 shows that this was not the case :

| | Samples of serum. | Serum dilutions. | | Total agglutinations. |
|--------------------------------|-------------------|------------------|------------------|-----------------------|
| | | 1 : 8 | 1 : 16 1 : 32 | |
| Group I. Acute rheumatic fever | 134 | 23 | 15 | 28 per cent. |
| " II. Rheumatoid arthritis | 104 | 16 | 9 | 24 " |
| " III. Other arthropathies | 60 | 10 | 8 | 30 " |

Agglutination tended to occur most frequently in sera taken during the active phase of acute rheumatic fever and acute rheumatoid arthritis, but

was by no means so limited. A suggestion that cases with acute joint involvement, as distinct from carditis, showed a fairly high incidence of agglutination may be of possible significance in explaining its occurrence with the sera of patients in Group III. The following summary illustrates this point where the data approach statistical significance:

Acute Rheumatism and Active Rheumatoid Arthritis.

| | Samples of serum. | Agglutination. | | Probable error. |
|-------------------------|-------------------|----------------|----------------------|-----------------|
| | | Positive. | Percentage positive. | |
| Total sera examined | 219 | 78 | 35.6 | |
| Activity | 171 | 68 | 39.8 | ± 2.5 |
| Recovery and quiescence | 48 | 10 | 20.8 | ± 3.9 |
| Recovered only | 19 | 1 | 5.3 | ± 3.5 |

Relation of agglutination reaction to clinical course. Analysis of the cases of monocyclic type shows that agglutination was not confined to the phase of recovery, but occurred during other phases as well. In view of this absence of uniformity it cannot safely be postulated that agglutination during the phase of recovery is a true expression of an immune response to a primary infective process. Agglutination occasionally appears to be related to the cycles in polycyclic rheumatic fever, which may occur every two or three weeks. While the correlation of experimental data and clinical observations on these cases at times favoured this view, the evidence is on the whole inconclusive. It is possible that sampling at intervals of not more than three days might have clarified this point, but this was impracticable. In most cases in Group I and many in Group II, especially those of so-called 'focal arthritis' and 'multiple infective arthritis', samples of serum were taken at frequent intervals over a period of many weeks, so that phases of intense rheumatic activity and moderate quiescence were investigated fairly thoroughly. In a few cases in the whole series there appeared to be some evidence of a coincidence between the curve of agglutination and the clinical course, but in others the coincidence occurred at some quite different phase in activity or quiescence. This general lack of consistency, therefore, makes it impossible to draw any definite conclusion that agglutination and clinical episodes are intimately related.

Relation of elementary body agglutination to streptococcal infection. Elementary body agglutination does not depend on the presence of *Streptococcus pyogenes* in the throat, nor does it necessarily occur after acute infection with *Streptococcus pyogenes* even when an attack of acute rheumatism is unquestionably related to the throat infection. In one instance, however, the simultaneous appearance of the ability of the serum to agglutinate rheumatic suspension at the onset of rheumatic fever following an acute throat infection was particularly striking. No reason for the behaviour of the serum in this isolated case can be offered.

Intercurrent *Streptococcus pyogenes* episodes were observed during hospitalization in six of the 54 cases studied. They have not been included in

the bacteriological data shown in Table I (columns 11 and 12) except when followed by a rheumatic attack in a previously inactive case. The streptococcal immunological findings (columns 6 to 10) in all six patients were undoubtedly influenced by these infections. Three of these were cases of acute rheumatic fever, two of which subsequently developed acute exacerbation of rheumatism, one focal arthritis, and two 'other arthropathies'. Intercurrent infection in these two cases accounts for five of the six readings between 250 and 312 units in the group of 'other arthropathies'.

Agglutination of elementary body suspensions occurred with serum giving antistreptolysin titres below 50 units on 14 occasions and below 100 units on 18. When history, bacteriological findings, and antistreptolysin titres on the same patients are considered, these readings provide convincing evidence that the patients were not at the time suffering from nor had, during the preceding three months, suffered from *Streptococcus pyogenes* infection. Agglutination occurred with 20 samples of serum giving titres in the equivocal range (100 to 200 units). In seven cases subsequent changes in the patients' antistreptolysin titre suggested that the earlier titres indicated streptococcal infection. In the remaining 13 cases there was no evidence of a streptococcal factor. Thus 31 of 110 agglutination reactions were with sera in which the balance of evidence was against an associated streptococcal infection. The fact that the majority of sera giving agglutination also gave antistreptolysin titres suggestive of streptococcal infection is merely a reflection of the intimate relationship between *Streptococcus pyogenes* infections, rheumatic fever, and some cases of multiple infective arthritis of unknown cause.

Assuming elementary body agglutination and antistreptolysin to be unrelated, the calculated expectation in the present series is that 30 of any 110 samples would show no evidence of streptococcal infection. There is, therefore, no evidence for a specific causal relationship between agglutination of rheumatic elementary body suspensions and streptococcal infection.

Relation of agglutination to erythrocyte sedimentation rate and pyrexia. There is no evidence that agglutination is dependent upon or influenced by conditions governing increased sedimentation rate or pyrexia. This confirms the earlier observations of Schlesinger, Signy, Amies, and Barnard (1935), and Eagles, Evans, Fisher, and Keith (1937).

Discussion

There can be little doubt that the sera from patients with acute rheumatic fever agglutinate suspensions prepared from the virus-like bodies present in the pericardial exudates of true rheumatic fever, and that normal sera and sera from a number of unrelated diseases do not. Whether this can be accepted as undoubted evidence that these suspensions contain true virus elementary bodies is questionable, particularly in view of repeatedly unsuccessful attempts by many workers to demonstrate any infectivity by

exudates or suspensions prepared from them. This may be because man alone is susceptible, or that these particles are inert and have no infective properties. This failure has naturally led to wider investigation of the problem in the hope of elucidating the nature of the factors responsible for the agglutination. It was at first thought that the reaction was confined to acute rheumatic fever, but it has been shown that it occurs with equal frequency with sera from acute rheumatoid arthritis and rheumatic chorea. This, considering the clinical overlapping of these diseases and rheumatic fever, was not surprising. There is seldom any serious difficulty in the diagnosis of typical cases of true rheumatic disease. But there are many examples where the chief presenting symptom is joint pain, even when infective arthritis is excluded, which cannot be fitted into any accepted classification of rheumatism in spite of the common factor of joint involvement.

In the present study this group of cases has been utilized to test how far the agglutination of suspensions from exudates of rheumatic fever can be said to be confined to the sera of rheumatism in the accepted clinical sense. Comparison of the incidence of agglutination by sera in this group with those of rheumatic fever and arthritis of the rheumatoid type shows that it is about equal in all three groups. Two interpretations may be offered. If the suspensions used for agglutination are of true virus particles, the virus of rheumatism must be much more widely distributed in man than is generally supposed, as reflected by the agglutination content of sera. It may be argued that the true virus particles are to be found only in the exudates of acute rheumatic fever in its fulminating form. This type is confined almost entirely to childhood and early adolescence. There is no support for such a view on clinical grounds, although from analogy with known infective agents it is to be expected that relatively more virus would be present under such conditions. It is only reasonable to assume, however, that considerable amounts of virus would be present in any rheumatic pericarditis or pleurisy of appreciable extent. In this connexion it is of fundamental importance to draw a sharp distinction between the true inflammatory exudates and simple transudates which frequently appear in the terminal stages of a fatal rheumatic carditis. Such a distinction is often extremely difficult, and confusion in research of this type can be avoided only by confining the suspensions used to those obtained from pericardial and pleural fluids withdrawn during life in the early stages of active inflammation or to post-mortem specimens in which the nature of the effusion is evident. It has been disappointing in our experience to find that as a rule relatively little particulate matter is present in exudates withdrawn during life under the circumstances indicated. It may be that at this stage the 'virus' is to a large extent intracellular. Although several suspensions were used and frequently compound ones were employed during the course of the investigations, it is reasonable to assume that they were as representative of the particle content of rheumatic exudates in general as is possible.

The alternative suggestion is that the so-called 'virus-bodies' in rheumatic exudates are not true elementary bodies as understood in known virus diseases, but have their origin in tissue and blood elements arising under abnormal physical conditions of which rheumatism is a striking example. The present work does not offer any proof of this conception; nor is the suggestion a new one. Several examples may be recalled in which substances, not themselves the infecting agent, are elaborated, are intimately related to particular infections, and are reflected in serum tests. The observations of Hughes (1933) in yellow fever, in which a precipitation occurred between serum of a recovered monkey and its own serum during an acute attack, although the precipitinogen was shown not to be the virus, and that of Rivers, Ward, and Smadel (1939) in which a soluble antigen present in serum of rabbits ill with infectious myxoma reacted with immune rabbit serum, may be quoted. Although there is no evidence as yet that agglutination of suspensions in rheumatism is related to episodes of streptococcal infection, methods of approach along the lines of Tillet and Francis (1930) with a non-nitrogenous fraction extracted from pneumococci, which was precipitated by sera from acute pneumonia, from the pyrexial stages of rheumatic fever, and from acute streptococcal and staphylococcal infections, may assist in elucidating any relationship which may exist. Schlesinger, Signy, Amies, and Barnard (1935) attempted unsuccessfully to relate the agglutination of rheumatic suspensions to increase in serum globulin and fibrinogen in a number of sera from the late stages of pregnancy. A preliminary report of observations by Bradley (1938) is interesting in its possible bearing on the phenomenon. He has found that during an attack of rheumatic fever there is an increased volume of plasma accompanied by a relative and absolute increase in circulating globulin and fibrinogen. He also suggests that there are qualitative abnormalities in the proteins. It is not known in how far these changes are confined to acute rheumatic fever, but they appear to be different in character from the blood-volume changes found in simple congestive heart failure. Coburn and Pauli (1939) have described a precipitin reaction which occurs between sera taken just before and shortly after the onset of acute rheumatism, and recurring with repeated rheumatic cycles. They consider the reaction distinct from the precipitation of pneumococcus C substance and from that of certain of the streptococcal antigens, although the possible importance of streptococcal infection in producing the reaction is by no means exhausted. Such observations may have no bearing upon the nature of the particulate matter derived from rheumatic exudates or their subsequent agglutination, but it is difficult to ignore them, particularly when it is remembered that exudates are derived chiefly from elements of the blood stream. The flocculation of particulate matter derived from the exudates by sera taken from patients in all phases and interphases of rheumatic infection might quite reasonably be closely related to the precipitation described by Coburn and Pauli. The agglutination of suspensions prepared from rheumatic exudates is now being

investigated from this standpoint. The fact that rheumatic suspensions are not agglutinated by normal sera, and that non-rheumatic suspensions are unaffected by rheumatic sera, suggests that some altered condition of this nature not as yet understood may be significant. Such a condition does not appear from our experiments to depend on the streptococcal infection which is of undoubted significance in rheumatic fever. In rheumatoid arthritis the connexion between streptococcal infection and the incidence of joint manifestations is less striking, and in the unrelated arthropathies there is rarely any such relationship. The occurrence of agglutination with the sera in these groups is additional evidence that streptococcal infection is not the deciding factor in the occurrence of the reaction. We have, however, not excluded beyond question the possibility of a streptococcal factor. How far the finding of a high incidence with the sera of acute rheumatic fever during the phase of joint involvement may explain the agglutination in the other groups where some joint involvement is a common factor is, at present, a matter of conjecture.

Summary

1. The sera of 54 patients, with joint pain as a common presenting symptom, and suffering from either rheumatic fever, arthritis of the rheumatoid type of unknown aetiology, or arthropathies not classified as true rheumatism, have been tested for agglutination with suspensions of rheumatic elementary bodies.

2. Agglutination has been elicited equally well in all three groups. The serum of each case has been tested at frequent intervals throughout the clinical course of the disease and particular attention paid to alterations in the clinical picture, including episodes of streptococcal infection. No consistent relation of agglutination of suspensions of elementary bodies to clinical phases has been found, nor is there any evidence that it runs parallel to antistreptolysin titre or erythrocyte sedimentation rate.

3. The occurrence of agglutination with the sera of patients in the group of 'unrelated arthropathies' is discussed with reference to the possible essential nature of the phenomenon as applied to rheumatism and the available evidence for the virus theory of aetiology.

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THE CEREBRAL BLOOD-FLOW IN ARTERIAL HYPERTENSION, ARTERIOSCLEROSIS, AND HIGH INTRACRANIAL PRESSURE¹

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THE fundamental importance of an adequate blood-supply to the brain is reflected in the extreme constancy of the cerebral circulation during health. Although the oxygen saturation of the blood leaving the brain is lower than that leaving the limbs, it is also much more stable. In observations on 167 cases (Lennox, 1936), not only was the deviation from the mean of samples extremely small, but repeated samples from the same subject also showed stability. The total cerebral blood-flow was found to have no causal relationship to sleep (Gibbs, Gibbs, and Lennox, 1935), or to epilepsy (Gibbs, Lennox, and Gibbs, 1934), but its experimental reduction below a critical level resulted in unconsciousness (Lennox, Gibbs, and Gibbs, 1935). Arteriosclerosis, arterial hypertension, or high intracranial pressure might modify cerebral blood-flow, and indeed symptoms such as headache, mental confusion, and coma which might accompany these conditions have been ascribed variously to cerebral engorgement and to cerebral anoxia. These explanations seem reasonable, but there has been little experimental evidence to support them. An attempt has therefore been made to compare the relative cerebral blood-flow of suitable groups of patients with that of a normal series.

Methods

The subjects of investigation were patients in the Boston City Hospital. Seven had no evidence of cardiovascular disease, had a normal cerebrospinal fluid pressure, and were set aside as a 'normal' control group. To this group were added 34 similar cases of the series reported by Lennox and Gibbs (1936). Forty patients had one or more of the named abnormalities; 21 having arterial hypertension, 18 signs of cerebral arteriosclerosis, and 13 an abnormally high intracranial pressure. Twelve of the abnormal subjects were included in two of the pathological groups. In normal and abnormal cases blood was taken from both an internal jugular vein and an artery, and the results are based on the differences of the gaseous content of artery and vein. In addition, blood from an internal jugular vein alone

¹ Received March 4, 1939.

was obtained in 12 control and 15 abnormal cases (of whom five had increased intracranial pressure, four arterial hypertension, and six cerebral arteriosclerosis).

Observations were made on each case under standard experimental conditions. The subjects, who were lying quietly in bed, had not taken food for over three hours, and had been resting during that time. All the observations were made in the morning. After the procedure had been explained to the patient, the skin just anterior to the mastoid tip was cleaned and infiltrated with 2 per cent. novocaine. An 18-gauge needle was then inserted into the jugular vein at its place of exit from the skull. Time was allowed for the subject to recover from the slight disturbance caused by the venepuncture, and then blood was removed without stasis, and transferred under oil to a chilled oxalated tube. A sample of blood was taken from the radial or brachial artery. Immediately before venepuncture the blood-pressure was measured by sphygmomanometry and, in those subjects with raised intracranial pressure, lumbar spinal fluid pressure was read in the recumbent position shortly before or after the blood sample had been obtained. The oxygen and carbon dioxide contents of the blood samples were determined, immediately after withdrawal, with the portable manometric gas apparatus and by the method described by Van Slyke (1927).

Selection of cases. The lowest blood-pressure reading in the hypertensive group was 160/90 mm. Hg and the highest 260/140 mm. Hg. The patients with cerebral arteriosclerosis had little or no increase in blood-pressure, and the diagnosis had been made independently by a physician on the basis of progressively advancing mental deterioration and amnesia, associated with signs of peripheral and intra-ocular arterial degeneration. Some of these cases showed the residual signs of cerebral thrombosis. The patients with raised intracranial pressure had lumbar spinal fluid pressures varying from 180 to 650 mm. of water, the results of intracranial tumour, trauma, or infection.

Results

The average ages, blood-pressures, and spinal fluid pressures of the subjects of the present investigation, excluding those already reported (Lennox and Gibbs, 1936), are listed in four groups in Table I. The average measurements of the gaseous content of arterial and internal jugular blood of the 81 subjects from whom both arterial and internal jugular blood was obtained, together with the arteriovenous differences and coefficients of utilization of oxygen and production of carbon dioxide, are shown in Table II. The average oxygen content of the arterial blood showed distinct differences in the four groups, being highest (18.29 volumes per cent.) in the group with high intracranial pressure, and lowest (16.69 volumes per cent.) in the group with high arterial pressure. These differences are a reflection of the number or concentration of red-blood cells in the different groups. Some of the patients

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with high cerebrospinal fluid pressure were receiving dehydration treatment, or were dehydrated as the result of their cerebral lesion. Their average oxygen capacity was 20.07 per cent. The average oxygen capacity of the hypertensive group was 18.34, of the arteriosclerotic group 18.70, and of the control group 18.90 per cent. Therefore, in order to take into account these

TABLE I

Average Measurements in the Three Groups of Patients

| Group. | No. of patients. | Average age. | Blood-pressure. | | C.S.F. pressure mm. of water. |
|----------------------------|------------------|--------------|---------------------|----------------------|-------------------------------|
| | | | Systolic mm. of Hg. | Diastolic mm. of Hg. | |
| Normal | 19 | 34 | 127 | 75 | 120 |
| High C.S.F. pressure | 23 | 43 | 150 | 88 | 323 |
| High blood-pressure | 25 | 53 | 196 | 110 | 160 |
| Cerebral arterio-sclerosis | 19 | 64 | 143 | 75 | 167 |

TABLE II

Average Gaseous Content of Blood in Subjects Having both Arterial and Jugular Puncture

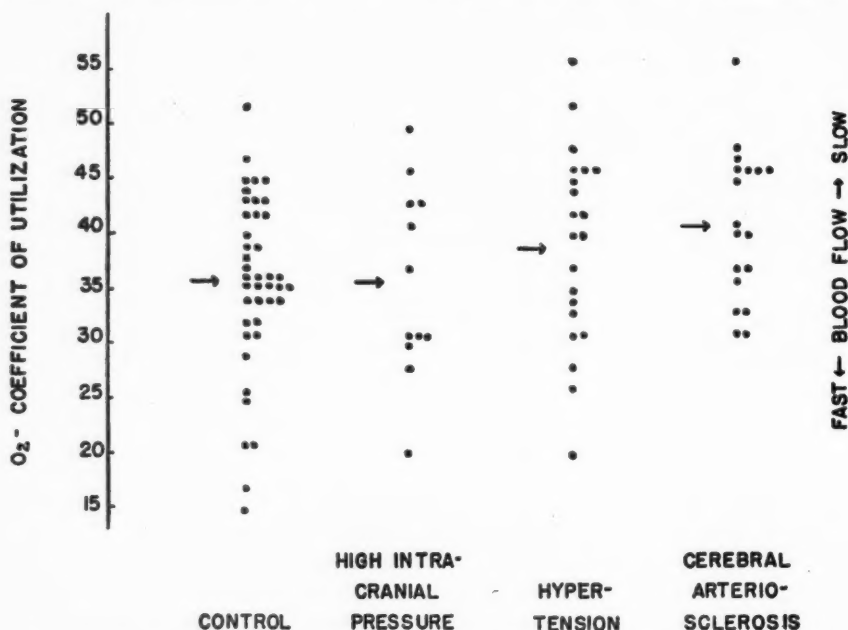
| Group. | Oxygen. | | | | Carbon dioxide. | | | |
|----------------------------|----------------|--------------------------|-------------------------------|------------------------------|-----------------|--------------------------|-------------------------------|-----------------------------|
| | Content. | | <i>a-v</i> difference vols. % | Coefficient of utilization % | Content. | | <i>a-v</i> difference vols. % | Coefficient of production % |
| | Artery vols. % | Internal jugular vols. % | | | Artery vols. % | Internal jugular vols. % | | |
| Control | 18.00 | 11.6 | 6.40 | 35.6 | 48.8 | 54.5 | 6.00 | 12.7 |
| High C.S.F. pressure | 18.29 | 11.68 | 6.61 | 36.3 | 45.55 | 52.80 | 6.81 | 14.9 |
| High blood-pressure | 16.69 | 10.21 | 6.48 | 38.8 | 46.63 | 53.75 | 7.12 | 15.2 |
| Cerebral arterio-sclerosis | 17.11 | 10.07 | 7.04 | 41.1 | 46.13 | 52.73 | 6.60 | 14.3 |

uncontrollable variations in the available oxygen of the arterial blood, the coefficient of utilization (the arteriovenous difference $\times 100$ divided by the arterial oxygen content) was calculated. This calculation permits a more accurate comparison of the various groups, and is more reliable than the arteriovenous difference when dealing with a grouped series of patients. It will be referred to later. Both the average and individual measurements of the coefficient of oxygen utilization are shown in the Figure. The determinations from individual cases are shown in Tables III, IV, and V.

In the group with increased intracranial pressure the coefficient of utilization of oxygen was almost the same as in the control group. The arteriovenous difference was relatively larger than the coefficient of utilization because of the relatively high oxygen content of the arterial blood. Most of the subjects in this group had intracranial neoplasms and—intentionally or unintentionally—were dehydrated.

In the group with high blood-pressure, the coefficient of utilization was relatively greater than the arteriovenous difference because the oxygen

content of arterial blood in this group was unusually low. The 'utilization' of oxygen was only 9 per cent. greater than in the control group, in contrast to the observation of Raab (1931) who reported that the average oxygen utilization was 23 per cent. greater in 10 patients with arterial hypertension than in control patients. Raab believes that the abnormally low content of



Distribution of measurements of the coefficient of utilization of oxygen in patients of various groups. The arrows indicate the average measurement for each group. As noted at the right of the figure, the higher coefficients indicate a slower rate of cerebral blood-flow.

oxygen in the internal jugular vein (high 'utilization') indicates an obstruction of the cerebral flow, the result of vasomotor spasm or sclerosis of cerebral vessels, and that the resulting anoxia of vasomotor centres in the brain leads to generalized hypertension. On the other hand, Weiss (1938) did not find abnormal levels of oxygen content of internal jugular blood in a small group of patients with hypertension.

The group of patients with evidence of cerebral arteriosclerosis showed a more definite deviation from the control group. The oxygen arteriovenous difference was 7.04 per cent., a 10 per cent. increase over the control group, and the oxygen utilization was 41.1 per cent., an increase of 15 per cent. This deviation, when assessed statistically, using Fisher's (1932) method for small samples, does not fall below the limits of a chance variation.

Consideration of the distribution of individual measurements indicates the cause of the small variations of the average of each group from normal. Inspection of the Figure or of the Tables shows that the relatively high

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oxygen utilization in the arteriosclerotic group is not due to many high values, but to the presence of only few patients with a low utilization. Seventeen per cent. of the normal controls had an oxygen utilization below

TABLE III
Patients with Increased Intracranial Pressure

| Case. | Age. | C.S.F. pressure mm. of water. | Blood-pressure mm. of Hg. | Oxygen. | | | Carbon dioxide. | | |
|-------|------|----------------------------------|------------------------------|-------------------|----------------------------|---------------------------------|-------------------|----------------------------|---------------------------|
| | | | | Content. | | Coefficient of utilization % | Content. | | a-v difference vols. % |
| | | | | Artery vols. % | Jugular vein vols. % | | Artery vols. % | Jugular vein vols. % | |
| Bet. | 21 | 390 | 120/80 | 13.98 | 7.02 | 6.96 | 49.77 | 51.1 | 7.10 |
| Pap. | 16 | 400 | 130/80 | 22.81 | 12.98 | 9.83 | 43.07 | 47.69 | 10.40 |
| Nag. | 31 | 240 | — | 16.01 | 9.05 | 6.96 | 43.45 | 39.82 | 8.52 |
| Wal. | 50 | 500 | 160/98 | 21.47 | 17.14 | 4.33 | 20.18 | 45.65 | 6.50 |
| Ste. | 24 | 450 | 108/60 | 18.27 | 12.61 | 5.66 | 30.95 | 52.13 | 0.27 |
| Dow. | 56 | 290 | 130/70 | 19.72 | 11.52 | 8.20 | 41.58 | 48.38 | 5.70 |
| McW. | 50 | 240 | — | 13.48 | 7.89 | 5.59 | 41.47 | 40.9 | 5.49 |

TABLE IV
Patients with Arterial Hypertension

| Case. | Age. | C.S.F. pressure mm. of water. | Blood-pressure mm. of Hg. | Oxygen. | | | Carbon dioxide. | | |
|-------------------|------|----------------------------------|------------------------------|-------------------|----------------------------|---------------------------------|-------------------|----------------------------|---------------------------|
| | | | | Content. | | Coefficient of utilization % | Content. | | a-v difference vols. % |
| | | | | Artery vols. % | Jugular vein vols. % | | Artery vols. % | Jugular vein vols. % | |
| Kil. | 63 | — | 230/150 | 17.38 | 9.33 | 8.05 | 43.9 | 52.4 | 8.5 |
| Tho. | 58 | — | 232/130 | 14.84 | 8.92 | 5.92 | 39.88 | 45.8 | 6.9 |
| McL. ² | 59 | — | 198/80 | 18.12 | 8.67 | 9.45 | 52.17 | 47.7 | 7.3 |
| Sho. | 51 | — | 180/112 | 18.31 | 10.58 | 7.73 | 42.21 | 53.5 | 7.9 |
| Vag. | 60 | — | 200/120 | 18.83 | 12.44 | 6.39 | 33.95 | 47.87 | 10.30 |
| Bry. | 65 | — | 180/60 | 14.45 | 8.07 | 6.38 | 44.15 | 25.15 | 5.66 |
| Fra. | 56 | — | 190/110 | 12.36 | 6.44 | 5.92 | 47.93 | 56.32 | 4.95 |
| Nan. | 55 | — | 218/100 | 18.19 | 12.15 | 6.04 | 33.20 | 47.4 | 16.03 |
| Har. | 50 | — | 260/140 | 19.97 | 16.0 | 3.97 | 19.88 | 47.3 | 5.51 |
| Cha. | 43 | — | 185/95 | 20.26 | 13.11 | 7.15 | 35.30 | 49.29 | 2.24 |
| Bul. | 62 | — | 200/115 | 16.85 | 12.46 | 4.39 | 26.07 | 55.27 | 4.69 |
| Ash. ¹ | 57 | 200 | 200/120 | 18.93 | 13.04 | 5.89 | 31.10 | 45.33 | 8.14 |
| Fer. ¹ | 29 | 220 | 220/120 | 12.27 | 8.78 | 3.49 | 28.44 | 55.33 | 6.17 |
| Kin. | 53 | 110 | 160/100 | 17.32 | 10.12 | 7.20 | 41.58 | 52.31 | 6.58 |
| Smi. ² | 73 | 160 | 170/90 | 19.60 | 10.76 | 8.84 | 45.10 | 44.35 | 8.51 |
| Tai. ² | 67 | 120 | 160/90 | 12.74 | 7.57 | 5.17 | 40.55 | 53.36 | 3.42 |
| Clu. ² | 71 | 100 | 180/100 | 16.75 | 8.96 | 7.79 | 46.50 | 43.60 | 11.37 |
| Law. ² | 58 | 120 | 168/110 | 13.48 | 7.18 | 6.30 | 46.70 | 38.15 | 5.78 |
| Eil. | 74 | — | 180/100 | 13.67 | 5.99 | 7.68 | 56.18 | 46.41 | 7.02 |

¹ Also in group of patients with increased intracranial pressure.

² Also in group of patients with cerebro-arteriosclerosis.

30 per cent., contrasting with none in the group of arteriosclerotics, so that none of these patients showed a cerebral blood-flow as fast as the flow of

17 per cent. of the persons with a normal cardiovascular system. An increase in flow, the systemic blood-pressure remaining constant, is associated with dilatation of the peripheral vascular bed, so that it is likely that mechanical rigidity of the peripheral vessels in these elderly arteriosclerotic patients prevented an increase in cerebral blood-flow. This is substantiated

TABLE V
Patients with Cerebral Arteriosclerosis

| Case. | Age. | C.S.F. pressure mm. of water. | Blood-pressure mm. of Hg. | Oxygen. | | | | Carbon dioxide. | | | |
|-------------------|------|----------------------------------|------------------------------|-------------------|----------------------------|----------------------------------|---------------------------------|-------------------|----------------------------|----------------------------------|----------------------------------|
| | | | | Content. | | | Coefficient of utilization % | Content. | | | <i>a-v</i> difference vols. % |
| | | | | Artery vols. % | Jugular vein vols. % | <i>a-v</i> difference vols. % | | Artery vols. % | Jugular vein vols. % | <i>a-v</i> difference vols. % | |
| Lan. | 55 | — | 110/72 | 18.33 | 9.72 | 8.61 | 46.97 | 47.5 | 54.2 | 6.7 | |
| Lev. | 63 | — | 114/80 | 17.65 | 11.75 | 5.90 | 33.41 | 47.5 | 54.4 | 6.9 | |
| San. | 73 | — | 140/80 | 18.43 | 11.71 | 6.72 | 36.45 | 48.9 | 55.6 | 6.7 | |
| Nel. | — | 160 | 130/76 | 17.98 | 10.70 | 7.28 | 40.47 | 48.78 | 54.78 | 6.00 | |
| Ell. ¹ | 63 | 290 | 140/80 | 22.10 | 11.90 | 10.20 | 46.18 | 41.96 | 50.6 | 8.64 | |
| Roc. | 60 | 100 | — | 16.71 | 8.66 | 8.05 | 48.18 | 47.08 | 51.96 | 4.88 | |
| Dia. ² | 43 | 240 | 200/120 | 20.29 | 13.95 | 6.34 | 31.24 | 40.58 | 47.11 | 6.53 | |
| McM. ¹ | 65 | 210 | 150/80 | 17.25 | 11.80 | 5.45 | 31.60 | 38.61 | 46.61 | 8.00 | |
| Bro. ² | 70 | 180 | 180/100 | 16.36 | 10.31 | 6.05 | 37.00 | 40.04 | 45.78 | 5.74 | |
| Hod. | 80 | — | 130/70 | 16.25 | 10.27 | 5.98 | 36.79 | 46.76 | 50.97 | 4.21 | |
| Sea. | 76 | — | 140/80 | 15.69 | 8.40 | 7.29 | 46.45 | 56.62 | 64.53 | 7.91 | |
| Gri. | 74 | — | 180/100 | 13.67 | 5.99 | 7.68 | 56.17 | 46.41 | 53.43 | 7.02 | |
| Seo. | 52 | 290 | 130/70 | 19.72 | 11.52 | 8.20 | 41.57 | 48.38 | 54.08 | 5.70 | |
| McE. | 54 | — | 110/72 | 14.95 | 10.05 | 4.90 | — | 51.92 | 56.71 | 4.79 | |

¹ Also in group of patients with increased intracranial pressure.

² Also in group of patients with increased intracranial pressure and arterial hypertension.

by the observation that inhalation of carbon dioxide or amyl nitrite does not produce the usual increase in cerebrospinal pressure in such cases. An unusual rigidity of the cerebral blood-flow in the arteriosclerotic group is suggested by inspection of the Figure, for values of oxygen utilization in this group, except for one high figure, lie between 28 and 48 per cent., whereas in the control group, except for one high value, the spread is between 15 and 47 per cent. In the case with an oxygen coefficient of utilization of 56 per cent., the arteriovenous difference was within normal limits, but the arterial blood was relatively unsaturated, thus causing the unusually high ratio.

It will be seen that the arterial carbon dioxide content is less than normal in all the abnormal groups, and is lowest in the group with high intracranial pressure. Reference to the individual figures in the Tables shows low carbon dioxide contents in a few cases, accounting for the decrease. The lower carbon dioxide readings are, however, reflected in the jugular carbon dioxide content also, the result being that the arteriovenous difference is unaffected. The respiratory quotient (carbon dioxide arteriovenous difference

divided by oxygen arteriovenous difference) of the four groups ranges round unity (from 0.94 to 1.10) showing a striking constancy in the face of other extreme variations. Lennox and Leonhardt (1931) found the average respiratory quotient of jugular blood of a large series to be 0.95.

Discussion

The difference in the oxygen content of the blood entering and leaving the brain depends on the rate of oxygen consumption of the brain and the rate of blood-flow through it. The terms oxygen 'uptake' or 'utilization' suggest that the blood-flow does not modify this difference. If the cerebral oxygen uptake were the same in all the subjects examined, the arteriovenous difference in the oxygen content would be a direct reflexion of the speed of the cerebral blood-flow. It is obvious that there must be a quantitative difference in cerebral oxygen utilization in individual cases, which will be determined largely by the ratio of cerebral tissue to the available vascular bed. In view of the number of cases used, it is likely that the average total cerebral oxygen requirement of the groups under discussion is similar. Any significant difference in the average arteriovenous difference of oxygen or carbon dioxide content would thus be the result of a difference in total cerebral blood-flow, high arteriovenous differences and high coefficients of utilization indicating diminished flow. For clarity the changes have therefore been expressed as far as possible in terms of alterations in flow.

Lennox, Gibbs, and Gibbs (1938) have suggested a mechanism whereby the cerebral circulation responds to changes in blood constituents, maintaining thereby a constant environment for cerebral cells. They have shown that the response of cortical potentials to such alterations are coincident with the changes in blood-flow, suggesting a causal relationship, the flow being adjusted to ensure an optimum environment for the cell. A slight increase in the arterial carbon dioxide pressure is immediately followed by rapid dilatation of cerebral arteries and arterioles. The blood-flow is thereby greatly increased, so that the arteriovenous difference in carbon dioxide falls, and the increase in arterial carbon dioxide is compensated for by a smaller unit contribution from the vessel. Conversely, a decrease in arterial carbon dioxide causes constriction of cerebral vessels, with slowing of cerebral blood-flow, and a consequent unit increase in carbon dioxide supplied by the cerebral substance, which has a high metabolic rate. Thus the carbon dioxide content of the blood in proximity to the nervous tissue is stabilized. The electrical activity of the brain responds much more rapidly to changes in carbon dioxide than to similar changes in oxygen or glucose, so that protection against fluctuations in carbon dioxide is more important than against the other variable blood constituents. In the present results this process is seen in groups of patients instead of in normal individuals under experimental conditions. In these groups, the average cerebral blood-flow

is normal, or nearly normal, in the face of gross factors tending to the contrary. Peripheral arterial hypertension might theoretically cause an increase in cerebral blood-flow, whilst arteriosclerosis without hypertension might so increase the cerebral arteriolar resistance that the flow would be diminished. Similarly, high intracranial pressure is reflected directly to the cerebral veins, so that the pressure of the venous blood rises. This, reflected to the capillaries, might result in stasis and a decreased cerebral blood-flow. Prinzmetal and Wilson (1936) have shown that a functional hypertonus of the peripheral vessels maintains the systemic blood-flow within normal limits in all types of hypertension, and Weiss and Ellis (1930) demonstrated that the resistance was increased in the peripheral arterioles. It is possible that a similar mechanism is present also in the cerebral vessels. In hypertension increase in blood-flow causing a decrease in carbon dioxide would cause constriction, increase in resistance, and diminished flow. In high intracranial pressure, however, the resulting high intracranial venous pressure having caused capillary stasis, and therefore diminished the blood-flow, results in an increase in the carbon dioxide tension at the periphery. This increase in carbon dioxide readily causes a dilatation of cerebral arterioles, and an increase in cerebral blood-flow.

Weiss and Frazier (1930) showed that the peripheral capillary counts of normal persons and of patients with hypertension and senile arteriosclerosis were normal, but in the last group the distribution of patent capillaries was much more irregular than in the other two groups, giving a 'moth-eaten' appearance. They could not exclude dropping out of capillaries, with resultant death of the surrounding tissue causing tissue shrinkage and an apparent equality of the capillary counts. The pathological picture of cerebral arteriosclerosis consists of small glial scars surrounded by normal cerebral tissue—a 'moth-eaten' appearance. This would presumably result in a decrease in total cerebral blood-flow. If there were a patchy anaemia of cerebral tissue, however, the accumulation of carbon dioxide in the neighbourhood of the areas of inadequate circulation would cause dilatation of surrounding arterioles and capillaries, so that the patchy deficiency in cerebral blood-supply would be effectively masked.

Four cases of high intracranial pressure in this series were in deep coma from which they could not be roused. Their average jugular oxygen content was slightly higher than normal (65.5 per cent.) and consequently the arteriovenous difference was lower (5.75 per cent.). This indicates an increased rather than a decreased cerebral blood-flow. Two patients had advanced cardiac muscle failure. One was cyanosed, and had venous engorgement, orthopnoea, and anasarca. His jugular blood was only 50 per cent. saturated, but because of his arterial anoxemia his arteriovenous oxygen difference was within normal limits. This level of oxygen saturation in the jugular vein is just above that which is associated with loss of consciousness (Lennox, Gibbs, and Gibbs, 1935). In the other subject with cardiac failure the jugular oxygen saturation was reduced to 48 per cent. In this case, also,

the arteriovenous difference was within normal limits. The cerebral blood-flow is therefore maintained within normal limits in high intracranial pressure with deep coma and in advanced heart failure.

In order to show that a significant alteration in cerebral blood-flow could be measured by this method, we observed cases of intracranial angiomata and vascular tumours. The patients were found to have a high jugular oxygen content, due to short-circuiting of arterial blood, and our procedure has been utilized as a diagnostic aid in attempting to differentiate intracranial aneurysms from angiomata.

Many theories which assume an alteration in cerebral blood-flow have been advanced to explain the symptoms of high intracranial pressure. The mental and physical symptoms accompanying cardiac muscle failure have been ascribed to insufficient oxygenation of cerebral blood. It has been said that hypertensive headache is due to distension of intracranial veins by increased blood-flow, and that the coma of high intracranial pressure is associated with cerebral anoxia. It would not be profitable to discuss them individually, but it is evident that the results of this investigation render these and similar hypotheses untenable.

Summary

1. Simultaneous samples of blood were obtained from an artery and from an internal jugular vein in 40 patients with high intracranial pressure, arterial hypertension, or cerebral arteriosclerosis, and from a control group of 41 persons without any of these disorders. The blood-gas contents were determined, and the arteriovenous differences and coefficients of oxygen utilization were used to estimate the relative cerebral blood-flow of the groups.

2. The total cerebral blood-flow of the groups with arterial hypertension and high intracranial pressure was normal.

3. The group with cerebral arteriosclerosis had a mean cerebral blood-flow of 15 per cent. below that of the control group. All the individuals in this group fell within normal limits, but none had a faster flow than the normal mean, due to mechanical limitation of the vascular bed.

4. It is therefore concluded that the cerebral blood-flow is not significantly altered by high intracranial pressure, arterial hypertension, or by cerebral arteriosclerosis without hypertension.

5. The mechanism whereby the cerebral blood-flow is maintained at a constant level in spite of extreme factors tending to the contrary is discussed.

We wish to thank Miss Ruth Herwitz and Mrs. E. L. Gibbs, who carried out the blood-gas determinations, and the medical staff of the Boston City Hospital for permission to investigate patients under their care. This work was done while Dr. Williams held a Rockefeller Travelling Fellowship in Neurology.

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THE EFFECT OF PITUITARY THYROTROPIC EXTRACT IN SUBJECTS WITH LOW BASAL METABOLIC RATES¹

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With Plate 13

Introduction

THE relationship of the anterior lobe of the pituitary to the thyroid gland has not been extensively studied in man. Cushing (1912) was among the first to show that total hypophysectomy in dogs was followed by rapid involution of the thyroid. In more recent years, many investigators have demonstrated that the anterior lobe of the pituitary contains a hormone which stimulates the thyroid gland. In animals the effect on the thyroid of injection of pituitary anterior lobe extracts has been studied by several methods. Rowlands and Parkes (1934) tested the activity of anterior lobe extracts by their capacity to increase the weight of the thyroids of immature female guinea-pigs. Collip and Anderson (1934) used changes in the basal metabolic rate of hypophysectomized rats as an index of thyroid activity, while Heyl and Laqueur (1935) rejected indirect methods based on metabolism, and used the hyperplastic changes which occur in the thyroid gland for quantitative estimation of thyrotropic substance. Rawson and Starr (1938) measured alterations in the height of thyroid epithelium as a method of assay.

Direct methods of microscopy, or of weighing the thyroid gland, are not practicable in man, and most investigators have confined their observations to measuring the basal metabolic rate. Verzář and Wahl (1931) showed that anterior pituitary extract raised the basal metabolism in guinea-pigs with intact thyroids, but that, following total thyroidectomy, pituitary extract had no effect on metabolism. This raised the possibility that normal human subjects might show signs of stimulation of the thyroid gland, following injection of similar pituitary extracts, and that cases of myxoedema might fail to show such a response. Schittenhelm and Eisler (1932) and Eitel and Loeser (1932) were among the first to study the effects of a thyrotropic pituitary extract in human beings. Feuling (1934) obtained a rise of metabolic rate in 29 subjects, after injection of similar extracts. Starr (1935) reported that there was great individual variation in the response to the injection of thyrotropic extract in four normal patients, while two patients with congenital hypothyroidism and one with myxoedema failed to respond at all. Thompson, Taylor, Thompson, Nadler, and Dickie (1936) studied

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59 subjects with various disorders of the thyroid gland, and obtained a rise of basal metabolism in 32 after injection of pituitary extracts. Among those that showed no rise of metabolism after injection were four cases of myxoedema. Scowen (1937) confirmed the lack of response in six cases of myxoedema, but with the same pituitary extract produced a rise of metabolism in two normal subjects. The evidence available seems to show that in cases of myxoedema no response can be obtained to the injection of anterior pituitary extracts, but there appears to be considerable doubt as to the constancy of the response in normal subjects. The observation of lack of response to injected thyrotropic extracts in disease is of value only if it can be shown that the same extracts always produce the expected phenomena in normal persons.

The purpose of this paper is to describe and discuss the results of injection of thyrotropic pituitary extract into (1) subjects without disease of the endocrine glands, (2) subjects with myxoedema, and (3) certain subjects exhibiting low metabolic rates, but lacking the characteristic signs of myxoedema. It has been found necessary to divide this last group into two parts.

Methods

The preparation used throughout this investigation was Ambinon (Organon Laboratories), 1 c.c. of which contains 100 to 300 Heyl-Laqueur units of thyrotropic principle. One Heyl-Laqueur unit is half the daily dose that injected intraperitoneally on two successive days induces a given degree of thyroid epithelial development in at least 66 per cent. of test guinea-pigs, within forty-eight hours of the first injection. This preparation is extracted from the anterior lobe of the pituitary gland of hogs, and contains some gonadotropic principle which cannot be eliminated without diminishing the thyrotropic activity. The effects of intramuscular injection of this substance have been followed by three methods:

1. *Clinical observation.* Before injection, each subject received a full clinical examination, and the ease with which the thyroid gland could be palpated was estimated. During, and for some days following, the period of injection, the pulse and temperature were charted at four-hourly intervals. Daily observations were made on the sensations of the patient, the state of the skin, the prominence of the eyes, the presence of tremor, and the size of the thyroid gland.

2. *Estimation of urinary creatine.* It has previously been shown (Schrire and Sharpey-Schafer, 1938 a) that the injection of thyrotropic extract into normal subjects results in excessive elimination of creatine in the urine. The measures taken for the collection of urine and the method of estimation of creatine are described in the same communication.

3. *Estimation of the basal metabolic rate.*

Results

Normal subjects. Twenty-two patients, without any abnormality of the endocrine system, were investigated. They were, in nearly every case, suffering either from peptic ulcer, sciatic pain, or some surgical condition, and for the purpose of this paper will be referred to as normal subjects. The

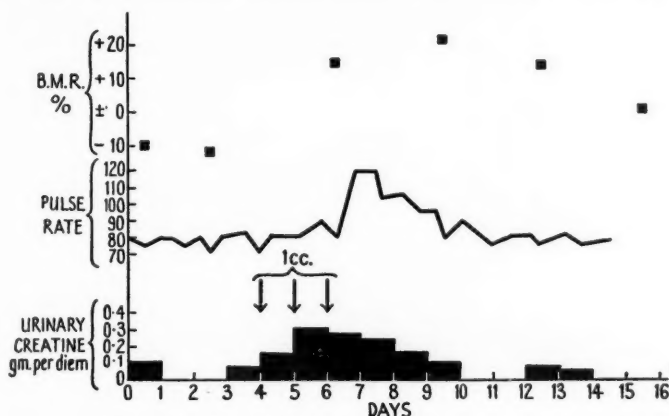


FIG. 1. Normal subject, response to thyrotropic extract; the arrows indicate the days of injection.

ages varied between 8 and 55 years; nine were males and 13 females. Without exception, all showed a response to the injection of thyrotropic extract, and a typical result is given in Fig. 1. As studied by the three methods outlined above, the following observations were made:

1. Clinical. Every subject, except two, complained of malaise. Headache was usual, and some tenderness was felt in the region of the neck. Every subject showed enlargement of the thyroid gland, as estimated by palpation, and usually the gland was tender to pressure. The pulse increased from 20 to 40 beats per minute. Six subjects had fever from 99.8° to 101° F. Sweating was often present, but exophthalmos was never observed and only three subjects had a slight tremor. The onset of symptoms was usually on the third or fourth day of injection, and on ceasing injection the symptoms rapidly subsided, so that in 48 hours the thyroid gland had returned to nearly its normal size, though the pulse-rate often remained rapid for several days longer.

2. Creatine was excreted in abnormal amounts in the urine.

3. The basal metabolic rate became elevated, the smallest rise being from 0 to +13 per cent., and the greatest from +3 to +46 per cent. The rise of metabolic rate appeared more variable than the clinical signs or the excretion of creatine; several subjects showed the maximum rise of metabolism on the sixth to tenth day after starting the injections.

The dose employed was that necessary to produce an adequate response. Fourteen subjects responded to the injection of 1 c.c. of thyrotropic extract

daily for three days, and in no case was it necessary to go beyond a daily dose of 1 c.c. for six days. Two subjects were given 3 c.c. daily for three days, and the effect was only slightly greater than that produced by the smaller dose. The results of this investigation showed that the response to thyrotropic extract can be judged adequately by clinical methods alone. Five subjects, with various disorders of the endocrine system, but with no

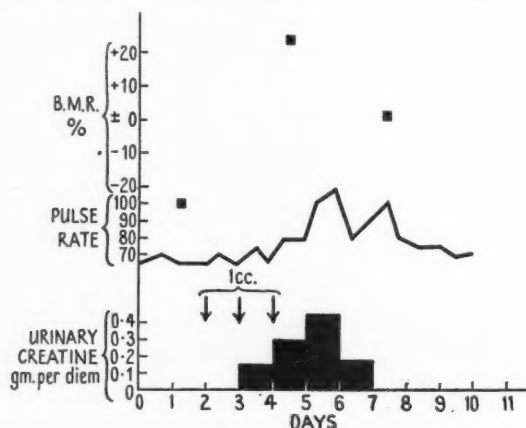


FIG. 2. Case 1, response to thyrotropic extract; the arrows indicate the days of injection.

evidence of thyroid disease, gave the same response as normal subjects when injected with thyrotropic extract. Of these patients two had prepubertal obesity, two had primary amenorrhoea, and one secondary amenorrhoea. In each case the basal metabolic rate, the electrocardiogram, the blood-cholesterol, and the circulation time were within normal limits.

Myxoedema. Three subjects with myxoedema, and one cretin, showed no response to the injection of thyrotropic extract. The subjects with myxoedema showed the classical signs and symptoms of the disease, the changes in the hair and skin being typical. In each case the electrocardiogram showed a low voltage with flat T waves, and an increased voltage was obtained on administering thyroid extract. The effect of injecting thyrotropic extract is shown in the Table. No alteration was observed in the clinical state, the creatine excretion, or the basal metabolic rate. The cretin, aged 9 months, also failed to respond to thyrotropic extract. This child had delayed appearance of the centres of ossification, the blood-cholesterol was 263 mg. per 100 c.c., and the electrocardiogram showed flat T waves, which were restored to normal voltage and appearance following the administration of thyroid extract. The metabolism, under standard conditions, was estimated in a closed chamber by measuring the carbon dioxide production, the result being -22 per cent., using Levine and Marples standards. Following the injection of 0.5 c.c. of the thyrotropic extract daily for three days, the metabolism was -24 per cent., and no change was noticed in the

clinical condition of the child. Subsequent administration of thyroid extract raised the metabolism to -1 per cent.

Low basal metabolic rate, normal response. Five subjects with a low basal metabolism responded normally to the injection of thyrotropic extract.

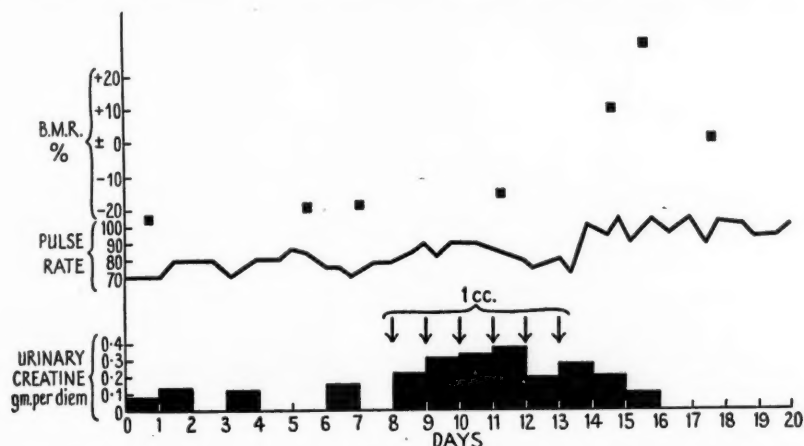


FIG. 3. Case 2, response to thyrotropic extract; the arrows indicate the days of injection.

Case 1. V. W., Male, aged 53 years. Psoriasis, osteitis deformans, and neurosis. Attacks of exhaustion for six years. Hands cold, suffers from chilblains. General examination otherwise negative. B.M.R. -26 per cent. Electrocardiogram and circulation time normal. Blood-cholesterol 197 mg. per 100 c.c. Osteitis deformans of both innominate bones. Blood phosphatase 61 units per 100 c.c. Response to thyrotropic extract (Fig. 2)—on the third day of injection complained of headache, sweating, and tightness of the throat; the thyroid was enlarged, and on the fourth day increased still further in size. The B.M.R. rose to $+22$ per cent. There was a return to normal a few days after the last injection, and the other cases in this series also returned to normal, on ceasing injection, in a similar time.

Case 2. H. E., Female, aged 29 years. Secondary amenorrhoea. Menstruation began at 14 years. Periods regular for four years, lasting two days. For ten years amenorrhoea. Hair and skin normal. Secondary sexual development and genitalia normal. Endometrial scrapings showed small stroma cells with atrophic glands. Visual fields, sugar tolerance curve, and X-ray of sella turcica normal. Electrocardiogram and circulation time normal. Epiphyses united. B.M.R. -22 per cent. Response to thyrotropic extract (Fig. 3)—on the third day of injection she felt ill; there was sweating and the thyroid gland was enlarged. The B.M.R. rose to $+29$ per cent.

Case 3. D. S., Male, aged 12 years. Prepubertal obesity. Family history not significant. Normal infancy. Always plump, had put on 30 lb. in two years. Carbohydrate intake excessive. Weight 126 lb., height 58 in. Obesity of face, breasts, abdomen, hips, and thighs. Genu valgum. Genitalia small for age; both testes descended. Skin and hair normal. Sella turcica and bone development normal. Response to thyrotropic extract (Fig. 4)—

on the fifth day the thyroid was enlarged. The B.M.R. rose from -27 to -1 per cent.

Case 4. J. S., Male, aged 12 years. Prepubertal obesity. Increasing obesity for two years. Family history negative. Fond of carbohydrate foods and consumes considerable quantities. Weight 131 lb. Obesity of face, trunk, and thighs. Hands and feet small. Genu valgum. Skin

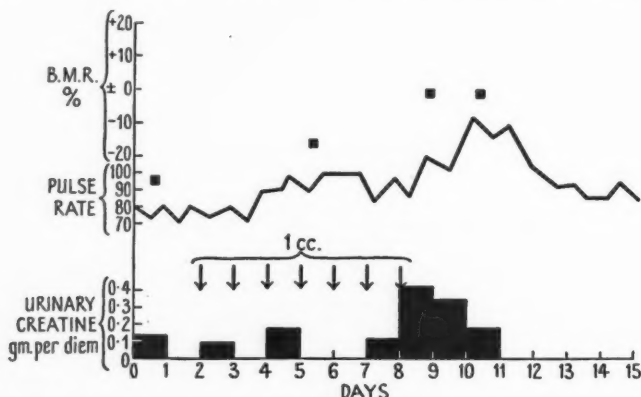


FIG. 4. Case 3, response to thyrotropic extract; the arrows indicate the days of injection.

smooth and fine, hair normal. Both testes were descended, but the left testis was small. Bone development normal for age. Sella turcica normal. The sugar tolerance test showed only a small rise of blood-sugar after the ingestion of 50 gm. of glucose. The blood-cholesterol was 162 mg. per 100 c.c. and the circulation time 12 sec. Electrocardiogram normal. B.M.R. -28 per cent. Response to thyrotropic extract—after 1 c.c. daily for five days the thyroid was enlarged, but the B.M.R. was -27 per cent. Two c.c. daily were given for two days. The thyroid increased in size, the pulse-rate rose from about 80 to 160, and the B.M.R. to $+20$ per cent. Creatine excretion was not followed in this case.

Case 5. A. G., Female, aged 15 years. Obesity. Healthy as a baby, and during early childhood. She was thin until the age of 7 years. She then became progressively more obese. Menstruation started at 12 years, and since then had been regular. She had a hearty appetite and consumed an excessive amount of carbohydrate food. Her father weighed 250 lb. She was the youngest of ten children, and her sisters were all plump. Weight 160 lb., height $62\frac{1}{2}$ in. Obesity of face, trunk, abdomen, and hips, the hands and feet being slender. There were numerous livid striae over the abdomen and thighs. The hair and skin were normal, and the secondary sexual characteristics were fully developed. The thyroid gland was slightly enlarged. The blood-pressure was 140/85 mm. of Hg. The electrocardiogram and circulation time were normal, and the blood-cholesterol was 287 mg. per 100 c.c. The sugar tolerance test showed a normal rise after 30 min., but did not return to the fasting level at the end of 120 min. X-rays showed a normal sella turcica, but there was premature union of the epiphyses for a girl of 15 years. Response to thyrotropic extract—1 c.c. of extract was given daily for six days; on the fourth day the thyroid was enlarged, and there was headache with malaise; on the fifth day the pulse

had risen from 80 to 120, and the B.M.R., which before injection was -29 per cent., had reached the level of +14 per cent.

Low basal metabolic rate. No response. Four subjects have been investigated who failed to respond to the injection of large doses of thyrotropic extract, although there is considerable evidence that they have functioning thyroid glands.

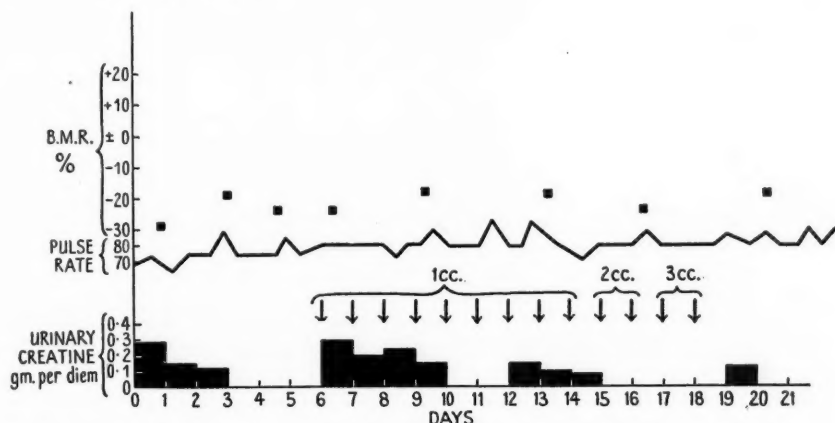


FIG. 5. Case 6, response to thyrotropic extract; the arrows indicate the days of injection.

Case 6. R. S., Male, aged 12 years. Prepubertal obesity. Normal birth, and healthy as a young child. Increasing in weight for two years. Mother moderately obese, maternal uncles and aunts tall and stout, father thin, and two siblings normal. Weight 129 lb., height 61½ in. (symphysis pubis to ground 32½ in.). Obesity confined to face, neck, trunk, and thighs. Skin fine and moist, and hair of fine texture. Eyebrows normal, no pubic or axillary hair present. The genitalia appeared under-developed for a boy of 12 years, but both testes were descended. The penis was 2.5 cm. long, and the testes 2.25 cm. in length. Genu valgum was present. The heart, lungs, abdomen, and central nervous system were normal. X-rays showed a normal sella turcica, and the centres of ossification and the epiphyses were normal for his age. The sugar tolerance, the electrocardiogram, the blood-cholesterol, and the circulation time were normal. The B.M.R. was -27 per cent. Starting on 4.4.38, 1 c.c. of thyrotropic extract was given daily for six days, and no change was observed in the clinical state, the B.M.R., or the excretion of urinary creatine. From 10.5.38 further injections of thyrotropic extract were given, at first 1 c.c. daily for nine days, followed by 2 c.c. for two days, and 3 c.c. for two days, a total of 19 c.c. over thirteen consecutive days (Fig. 5). Again no changes in the clinical state, the B.M.R., or the creatine excretion were observed. The urinary creatine shown in the chart was physiological. On 29.5.38, seven days after the last injection of thyrotropic extract had been given, a biopsy of the thyroid gland was obtained. At operation, by Mr. A. K. Henry, the thyroid appeared to be of normal size and consistency. The lateral lobes were not, however, fully exposed. A piece from the isthmus was taken for section. Report on histology of thyroid by Dr. J. Gray (Plate 13): 'The portion of

thyroid received shows no evidence of stimulation of activity. The great bulk of the acini are of moderate size, filled with deeply staining colloid and lined by cubical epithelium. There is, occasionally, a little folding and projection of the epithelium of an acinus, but the evidence of activity is within normal range. There is a very fine fibrosis separating many of the individual acini from one another.' Response to intravenous thyroxin—on

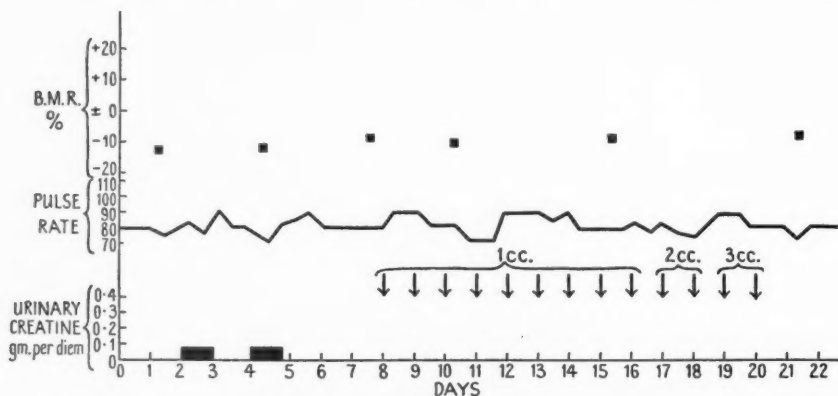


FIG. 6. Case 7, response to thyrotropic extract; the arrows indicate the days of injection.

5.10.38 the B.M.R. was -16 per cent., and on 7.10.38 15 mg. of crystalline thyroxin were injected intravenously. Two days later the patient was sweating and the pulse had risen from 70 to 100 beats a minute, and the temperature to 99.8° F. On 11.10.38 the B.M.R. was +2 per cent. It would appear, therefore, that this patient responded in a normal manner to the administration of thyroxin.

Case 7. M. F., Female, aged 16 years. Infantilism and dwarfism. At birth weighed 5½ lb., a breech delivery. Severely ill with pneumonia aged 3 weeks. Talked at 12 months, walked at 18 months, and appeared to be of normal size at this age. Aged 5 years was noticed to be under-sized, but was a bright and clever child. Aged 13 years was given thyroid extract 3 gr. a day for eighteen months. She had never menstruated. A sister, aged 28 years, died of pulmonary tuberculosis in a mental hospital. The mental illness of this sister had started at 14 years and she had never menstruated; she had slight development of the breasts. There were no other siblings. Previous generations appear to have been normal. On admission her weight was 84 lb. and height 55½ in. (symphysis pubis to floor 27½ in.). She was a bright intelligent girl. She was well covered with subcutaneous tissue, but was not obese. The skin was fine in texture and normally moist. The hair of the head was fine and abundant, and the eyebrows normal. There was no pubic or axillary hair. No breast tissue could be felt and the external genitalia were infantile. Vaginal examination showed a cervix and uterus that were only just palpable, consisting of a small button of tissue. Ovaries were not felt. Section of the vaginal mucosa showed areas where the epithelium appeared normal, and other areas where the epithelium was rudimentary and reduced to a few cells. In front of the trachea, some tissue was felt in the position of the isthmus of the thyroid gland. Heart, lungs, abdomen, and central nervous system

were normal. The electrocardiogram and circulation time were normal. The blood-cholesterol was 182 mg. per 100 c.c. X-rays showed a normal sella turcica, and that the union of the epiphyses was slightly delayed. The sugar tolerance test showed only a very small rise of blood-sugar following the administration of 50 gm. of glucose. The basal metabolic rate was -14 per cent. From 1.3.38, 1 c.c. of thyrotropic extract was injected daily

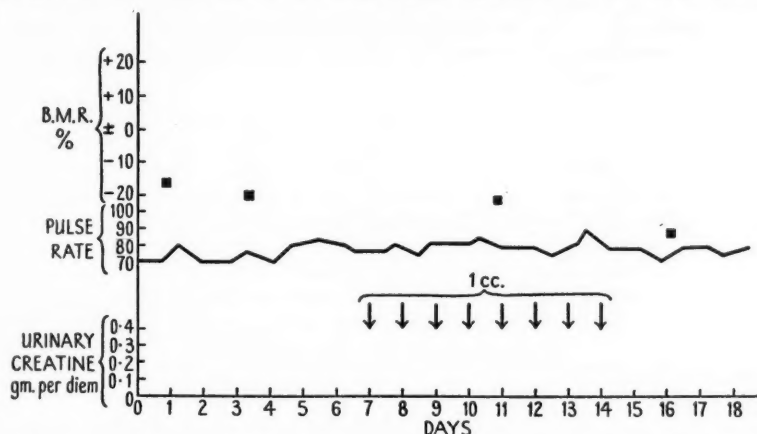


FIG. 7. Case 8, response to thyrotropic extract; the arrows indicate the days of injection.

for six days. No response was observed. From 10.5.38, 1 c.c. of the same extract was injected daily for nine days, followed by 2 c.c. daily for two days, and 3 c.c. for two days, a total of 19 c.c. over thirteen days (Fig. 6). Clinical observation showed no change. No excess of creatine was excreted in the urine. On the seventh day of injection the basal metabolic rate was -13 per cent., and on the fourteenth day -6 per cent. A biopsy of this patient's thyroid has not been obtained.

Case 8. B. F., Female, aged 22 years. Secondary amenorrhoea. After a normal childhood, started to menstruate at the age of 14. Her periods were normal for a year, the cycle being 3/28, but after the age of 15 they became gradually less frequent, and from the age of 16 to 21 she menstruated every three months. For nine months before admission there had been complete amenorrhoea. For six months she had felt lethargic, and had noticed an increase in weight. The family history was not significant. Weight 142 lb., height 67 in. The skeletal proportions were of the eunuchoid type, the limbs being long in relation to the trunk. The skin was greasy, and not noticeably dry. The hair of the head was normal, and the pubic hair scanty, but of normal feminine distribution. The eyebrows were somewhat defective in the outer third. The breasts were poorly developed. The external genitalia were normal. The uterus appeared to be small. No endometrium could be obtained on curettage. The thyroid gland could not be palpated. General examination was normal. X-rays of the skeleton showed delayed union of the epiphyses; the sella turcica was normal. The electrocardiogram showed normal P and T waves; the voltage of the QRS complexes was slightly low. The circulation time and sugar tolerance were normal. The B.M.R. was -22 per cent. From 18.3.38, 1 c.c. of thyrotropic extract was injected daily for eight days; no response was obtained

(Fig. 7). Following the administration of thyroid extract 3 gr. daily, the B.M.R. rose to +1 per cent., but no change had occurred in the electrocardiogram after six weeks' administration. Two points in this patient might suggest a diagnosis of early myxoedema, the defective eyebrows and the slightly low voltage of the QRS complexes in the electrocardiogram. The administration of thyroid extract, however, produced no change in voltage, so it is probable that these QRS complexes were not significant of thyroid deficiency. The delayed union of the epiphyses and the eunuchoid skeleton were considered to be due to lack of development of the gonads. Biopsy of the thyroid has not been obtained.

Acromegaly. Case 9. E. M. R., Female, aged 34 years. The case history and observations on the creatine-creatinine excretion of this patient have already been published (Schrire and Sharpey-Schafer, 1938 b). In 1933 the thyroid gland was found to be enlarged and a nodular goitre was removed in July, 1937. She has been continuously under observation since October, 1937. In addition to the typical findings of acromegaly, she was very hirsute, and sweating was pronounced. Some nodular tissue was felt in the region of the thyroid gland. The electrocardiogram and circulation time were normal. The blood-cholesterol was 370 mg. per 100 c.c. The B.M.R. varied between +12 and +26 per cent. An excess of creatine was excreted in the urine. From 2.1.38, 1 c.c. of thyrotropic extract was injected daily for three days; there was no response. From 6.10.38, 1 c.c. of extract was injected daily for nine days; no change took place in the clinical condition of the patient or in the basal metabolic rate. The excretion of creatine was not followed.

Discussion

The results obtained in normal subjects appear to be consistent. Factors, such as age and weight, might well be expected to produce a certain degree of variation. No attempt has been made to correlate the amount of pituitary extract needed to produce a response with either of these factors, though it was observed that the heavier patients needed a larger dose. Of the 22 normal persons investigated, not one was found to be refractory to the pituitary extract used, and the largest total dosage necessary to produce a response was 6 c.c. The variability of response reported by other workers (Starr, 1935; Thompson, Taylor, Thompson, Nadler, and Dickie, 1936) is possibly related to the potency of the extracts employed. Using our results in normal subjects as a control, the five subjects who had endocrine disorders, but apparently normally functioning thyroids and normal basal metabolic rates, responded in an identical way. The group of cases (1 to 5), in whom the basal metabolic rates were low, also responded in a normal manner. These cases had no signs of thyroid deficiency, except for a low basal metabolism, but in the present state of knowledge it is felt that the assumption that a low metabolism in itself signifies thyroid deficiency is unwarranted. There is no proof that the low metabolism in these cases is due to a lack of drive from the anterior pituitary, and all that can be inferred is that this group has thyroid glands that are capable of responding normally to the stimulus of injected pituitary thyrotropic extract, although

the cause of the lowered metabolism remains unknown. When a low metabolism results from the destruction of the anterior pituitary lobe and there is a loss to the organism of the drive of the thyrotropic principle, there is good evidence that the thyroid gland may still be stimulated, and a rise of metabolism produced, by the injection of suitable anterior lobe extracts.

TABLE

The Response to Thyrotropic Extract in Myxoedema

| Case. | Age. | Sex. | Circulation time in sec. | Blood- cholesterol mg. per 100 c.c. | B.M.R. before injection. | Thyrotropic extract. Total dose in c.c. | B.M.R. after injection. | Urinary creatinine. |
|-------|------|------|-----------------------------|--|--------------------------------|--|----------------------------|------------------------|
| H. M. | 63 | F. | 22.5 | 280 | -13 % | 8 | -14 % | 0 |
| H. R. | 50 | M. | 17.5 | 360 | -29 % | 12 | -32 % | 0 |
| E. T. | 45 | F. | 20 | 432 | -37 % | 15 | -35 % | 0 |

Collip and Anderson (1934) have demonstrated this in rats, and a similar response has been obtained in patients with Simmond's disease (Starr, 1935; Bulger and Barr, 1936; Scowen, 1937; Spence and Witts, 1939).

As expected, and confirming other workers (Starr, 1935; Thompson, Taylor, Thompson, Nadler, and Dickie, 1936; Bulger and Barr, 1936; Scowen, 1937) three cases of myxoedema and a cretin failed to respond to the injection of thyrotropic extract. Starr (1935) states that he obtained a response in a case of mild myxoedema, but according to Means (1937) spontaneous myxoedema is a state of complete 'athyreosis' and the severity of the disease is largely, if not entirely, related to its duration. Wachstein (1934), however, reported a case of great interest; a woman of 28 had symptoms of myxoedema, the basal metabolic rate was -28 per cent., and the electrocardiogram showed a low voltage curve with flat P and T waves. Following the administration of a pituitary thyrotropic extract, the metabolism rose to -2 per cent. and there was an increased voltage, with upright T waves, in the electrocardiogram. Further injection of thyrotropic extract was without effect, and in spite of continuation of the injections, the basal metabolism and the electrocardiogram returned to the untreated state. The effect of thyroxin, in this case, is not reported, nor is there any pathological evidence of the structure of the thyroid gland. If this represents a true response to thyrotropic extract, then this patient must presumably have had some functioning thyroid tissue left, and it is possible that, in the course of the development of the syndrome of spontaneous myxoedema, there may be found a stage when symptoms are present and there is still some thyroid tissue that will respond to stimulation; Wachstein's case may represent such a state of affairs. In the great majority of cases diagnosed as myxoedema and showing the classical signs and laboratory findings of the disease, it is probable that the view put forward by Means holds good; that they have complete 'athyreosis', and therefore will give no response to injected thyrotropic extract.

The subjects with low basal metabolic rates who did not respond to thyrotropic extract (Cases 6, 7, and 8) present a different and altogether unexpected problem. There is good evidence that these cases were not suffering from 'athyreosis', for in each case the clinical and laboratory findings of myxoedema were absent, and in one case a biopsy of the thyroid was obtained and showed a gland within the limits of normal. Yet the injection of large amounts of thyrotropic extract failed to produce any response. Certain possibilities need examination. A negative response must always raise the question of the potency of the preparation used. Ampoules of thyrotropic extract were taken at random from a large batch, and, during the investigation of these three patients, normal subjects were injected from the same batch, in every case with positive results. In addition, Cases 6 and 7 were injected on two separate occasions, at an interval of several months. There seems to be no reason to doubt the potency of the preparation used. That some normal individuals may fail to respond to thyrotropic extract might be suggested by the results of Thompson, Taylor, Thompson, Nadler, and Dickie (1936), but an explanation of their results has already been put forward, and no failure has been found in this series of normals. It is possible that cases with a low metabolism need more stimulation than those with a normal metabolism. This is unlikely, as the dosage employed to produce a response in both normals and Cases 1 to 5, who also had a low metabolism, was the same, and the dosage given to Cases 6, 7, and 8 was considerably greater. Scowen (1937), using the same preparation as employed in this investigation, gave even larger amounts of thyrotropic extract in myxoedema, though in this disease there would seem to be no limit to the amount that can be injected without response. It still remains possible that the dosage used in Cases 6, 7, and 8 was inadequate. A comparison, however, with the normal series of controls makes it probable that these cases are refractory to injected thyrotropic extract within the limits imposed by the nature of the experiment. The biopsy obtained in Case 6 is of considerable interest. The lack of definite signs of stimulation might be compatible with a gland that is resistant to the drive of the patient's own pituitary, and the evidence suggests that Cases 7 and 8 have similar thyroid glands, though histological proof is lacking.

The mechanism by which such thyroids resist injected pituitary extract is obscure. Anti-thyrotropic substances have been demonstrated in the serum of animals given thyrotropic hormone (Collip and Anderson, 1934). Such anti-substances have not yet been shown to occur naturally. Starr (1935) has suggested that in castrates the response to injected thyrotropic hormone is diminished. Starr and Bruner (1935), however, found that guinea-pigs, castrated for thirty days, showed the same response to injection as normal animals. Cases 6, 7, and 8 had one feature in common, that they all had a degree of gonadal deficiency. There may still be some relationship between the refractoriness and the state of the sex glands. If it is accepted that these cases have a real resistance to thyrotropic extract, then it is

possible that they are refractory to the drive of their own anterior pituitaries, and thus there is afforded an explanation for their lowered metabolism. The satisfactory demonstration of such a resistance would mean that low metabolism cannot be used as evidence of deficient pituitary function, though in similar cases with hypogonadism and so-called pituitary stigmata such an argument has been used.

The results in the patient with acromegaly, Case 9, are complicated by a previous partial thyroidectomy. Other cases of partial removal of the thyroid have not been investigated, but the presence of excess creatine in the urine and the slightly raised basal metabolic rate point to the presence of active thyroid tissue in this patient. It has previously been suggested (Schrire and Sharpey-Schafer, 1938 *a*) that the excess of creatine found in the urine in acromegaly may depend on stimulation of the thyroid by an over-active pituitary. Houssay (1932) has shown that the rat has a thyroid which is much harder to stimulate with pituitary extracts than the thyroid glands of other species, and the explanation given is that the rat's thyroid is normally in an extremely active phase. It is possible that the remaining part of the thyroid gland in this case of acromegaly was already working at its maximum, and thus failed to respond to thyrotropic extract.

These results show that a reliable preparation of thyrotropic extract may be used to investigate the function of the thyroid gland in man. Its further use may help to clarify that indefinite group of cases which have low basal metabolic rates, but lack other signs of thyroid deficiency.

Summary

1. The effects of intramuscular injection of pituitary thyrotropic extract have been studied by observations on the clinical state, the excretion of creatine in the urine, and the basal metabolic rate, in normal and abnormal subjects.

2. Each of 22 normal subjects investigated responded to the injection of thyrotropic extract. Five other subjects, with various endocrine disorders, gave a normal response.

3. Five subjects with low basal metabolic rates reacted in a normal manner.

4. Three subjects with myxoedema and one cretin failed to respond.

5. Three subjects, without evidence of thyroid deficiency, but with low basal metabolic rates, failed to respond to the injection of large doses of thyrotropic extract. In one case a biopsy of the thyroid showed a resting gland, with no evidence of increased activity. A case of acromegaly also failed to respond.

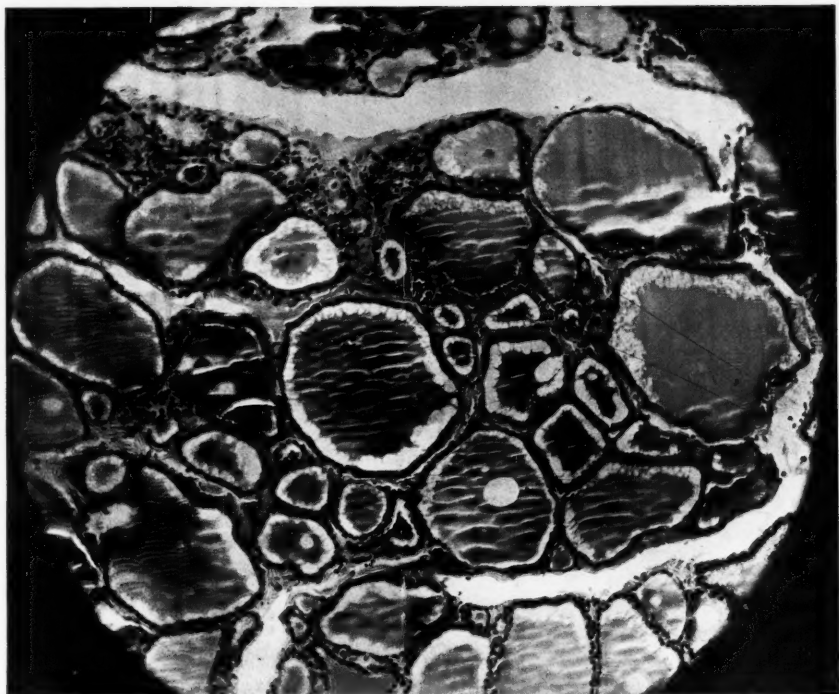
6. It is suggested that there are cases which are resistant to the stimulus of the thyrotropic principle, although they have functioning thyroid glands.

We wish to thank Mr. A. K. Henry and Dr. J. Gray for their help in

Case 6, and the Chief Medical Officer, London County Council, for permission to publish case records. To Dr. A. Macbeth of Organon Laboratories we are indebted for generous supplies of thyrotropic extract.

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Photomicrograph of the thyroid of Case 6. Magnification $\times 110$; section stained with haematoxylin and eosin

THE TREATMENT OF CHRONIC HYPOPARATHYROIDISM¹

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Introduction

THE treatment of parathyroid deficiency, whether the condition is the result of accidental removal of parathyroid tissue during extensive operations on the thyroid gland or occurs in the so-called idiopathic form, can be divided into two stages. The acute manifestations of the disease, of which the most characteristic are the spasms of tetany, usually yield readily to the intravenous injection of calcium salts, with or without the simultaneous intramuscular injection of parathyroid extract. Such parenteral therapy is not suitable, however, for the treatment of cases in which the condition of parathyroid deficiency is permanent, and these cases may present difficulties in management when an attempt is made to maintain the clinical condition and the blood chemistry in a state approximating to normal. Indications for the effective control of chronic hypoparathyroidism must be derived from physiological experiments on the effects of the removal of the parathyroids on the calcium and phosphorus metabolism of the organism. The hypocalcaemia which occurs in this condition is not due to increased excretion of calcium as was suggested by earlier workers (MacCallum and Voegtlin, 1909; Salvesen, 1923). On the contrary, the parathyroidectomized animal excretes less calcium than the normal, a finding confirmed in the dog by Greenwald and Gross (1925), in the rat by Bülbring (1931), and in man by Aub, Albright, Bauer, and Rossmeisl (1932). Nevertheless, the oral administration of calcium salts in large amounts has remained one of the most important forms of treatment of the hypocalcaemia of parathyroid deficiency.

That control of the phosphorus intake is perhaps of equal importance in the treatment of hypoparathyroidism is indicated by the experimental work relating to the disturbance of phosphorus metabolism found in this condition. Greenwald (1911, 1913) showed that parathyroidectomy in the dog led to a decrease in phosphorus excretion and a rise in the level of the inorganic phosphorus of the serum. The observation of Binger (1917) that the intravenous injection of phosphate solutions into normal dogs caused hypocalcaemia and tetany appeared to lend support to Greenwald's suggestion that retention of phosphorus in the body may be the primary metabolic

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disturbance in parathyroid deficiency. Greenwald's findings in the dog were confirmed in man by Albright and Ellsworth (1929) and Aub, Albright, Bauer, and Rossmesl (1932), who showed that clinical hypoparathyroidism is accompanied by hyperphosphataemia and a retention of phosphorus in the body, due to a decrease in its excretion in the urine. From their observations on the effect of injection of parathyroid extract in normal subjects, Albright, Bauer, Ropes, and Aub (1929) concluded that the primary action of the parathyroid hormone is on phosphorus rather than calcium metabolism, the first observed effect of injections of parathyroid extract being a marked increase in the amount of phosphorus excreted in the urine.

Ellsworth (1932) extended this conception of the action of the parathyroid hormone by suggesting that the primary function of the parathyroid hormone is to control the renal threshold for the excretion of phosphorus. He pointed out that hypoparathyroidism is characterized by a marked reduction in the urinary excretion of phosphorus in spite of the elevation of the level of serum inorganic phosphorus, whereas in hyperparathyroidism the urinary excretion of phosphorus is excessive in the presence of a lowered serum inorganic phosphorus. As evidence in favour of this theory, he mentioned the results of experiments in which he followed the excretion of calcium and phosphorus in the urine and the levels of these elements in the serum at hourly intervals after the injection of parathormone in patients suffering from parathyroid deficiency. The first effect of the injection was an immediate outpouring of phosphorus in the urine and a simultaneous fall in the raised serum inorganic phosphorus, while a rise in the low serum-calcium followed only after some hours. Ellsworth gives the following table of the changes produced by the parathyroid hormone, in the order of their appearance :—

1. Lowering of the renal threshold for phosphorus.
2. Increase in the urinary excretion of phosphorus.
3. Fall in the serum inorganic phosphorus.
4. Rise in the serum-calcium in adjustment to 3.
5. Increase in the urinary excretion of calcium as a result of 4.

In parathyroid deficiency, the conditions are reversed with :—

1. Rise in renal threshold for phosphorus.
2. Decreased urinary phosphorus excretion.
3. Rise in serum inorganic phosphorus.
4. Fall in serum-calcium in adjustment to 3.
5. Decreased urinary calcium as a result of 4.

Goadby and Stacey (1934) confirmed Ellsworth's observations and suggested that the parathyroid hormone either increased the capacity of the kidney to excrete inorganic phosphorus, or promoted an increased breakdown of inorganic phosphates by the phosphatase enzyme present in the kidney. It must be admitted that the above conception of the action of the parathyroid hormone has not received universal acceptance. In an extensive review of

the literature, Thomson and Collip (1932) favour the hypothesis that the parathyroid hormone acts primarily on the bones, causing liberation of calcium by some direct stimulating action on the osteoclasts. Pugsley and Selye (1933) were able to show that the hypercalcaemia and increased urinary calcium excretion, which was the first effect of daily injection of parathyroid extract into rats, coincided with a phase of increased proliferation of osteoclasts in the bones. The subsequent fall in urinary calcium excretion to normal or even subnormal levels which resulted from continued injection of parathyroid extract was accompanied by a disappearance of osteoclasts from the bones and a proliferation of osteoblasts. Collip, Pugsley, Selye, and Thomson (1934) demonstrated also that the typical picture of osteoclastic bone resorption can be produced in bilaterally nephrectomized rats by the injection of parathyroid extract.

In his monograph on diseases of the parathyroid glands, Shelling (1935) criticizes the previous theories as to the mechanism whereby the parathyroid hormone exerts its effect, and suggests an alternative explanation. He had previously shown (Shelling, 1932) that the calcium : phosphorus ratio of the diet was the factor which determined the onset of tetany in parathyroidectomized rats. In such animals, fed on a diet with a low calcium and a normal phosphorus content, or a normal calcium and a high phosphorus content, the serum-calcium fell, the serum inorganic phosphorus rose, and the animals developed tetany. If the animals were transferred to a diet with a high calcium and low phosphorus content, the serum-calcium rose, the serum inorganic phosphorus fell, and the animals became free of tetany. In later experiments, Shelling and Asher (1935) found that the rise in serum-calcium and fall in serum inorganic phosphorus which occurred when calcium was added in sufficient amount to the diet of the parathyroidectomized rat were accompanied by the excretion of the retained phosphorus by the bowel.

In reviewing the results of these experiments and the observations of other workers on the changes in calcium and phosphorus metabolism produced by excess or deficiency of the parathyroid hormone, Shelling (1935) concludes that the hormone undoubtedly increases the solubility of calcium phosphate in the blood. He points out that the physico-chemical factors which govern the solubility of calcium phosphate in the serum are: the pH, the carbon dioxide tension, the protein concentration, the total ionic strength of the serum, and the magnesium concentration. Since there is no convincing evidence that either injection of parathyroid hormone or parathyroidectomy affects the first three factors, Shelling suggests that the parathyroid hormone may increase the solubility of calcium phosphate in the serum (and urine) by increasing the total ionic strength and the magnesium concentration of these fluids. He points out that in hyperparathyroidism there may be a moderate hyperchloraemia, and that injection of parathyroid hormone in non-toxic doses causes a diuresis with an increased excretion of chlorides. Conversely, the excretion of urine in hypoparathyroidism is

decreased, and the blood chlorides and the serum magnesium are said to be low.

Shelling believes that the most important metabolic abnormality of the parathyroidectomized organism is its inability to excrete excess phosphorus in appreciable amounts through the kidneys, owing to the factors mentioned above. The resultant accumulation of phosphorus in the serum, together possibly with its decreased inactivation by magnesium, lead to the fall in the level of the serum-calcium. As far as possible, the parathyroidectomized organism prevents the accumulation of phosphate by increasing the excretion of phosphate in the faeces in the form of insoluble calcium phosphate; since a large part of the ingested calcium must be used in this way, the calcium requirement of a parathyroidectomized animal is greater than normal. On the basis of this theory, Shelling proposed that patients suffering from parathyroid deficiency should be treated by giving them a diet low in phosphate, along with a liberal intake of calcium. The lowered phosphate intake should minimize the amount of ingested calcium required in the excretion of phosphorus in the faeces as calcium phosphate, thus leaving sufficient absorbed calcium for the maintenance of a normal serum-calcium level. Shelling and Goodman (1934) showed, in two cases of post-operative tetany, that this treatment lowered the serum-phosphorus, raised the serum-calcium, and prevented tetany. One of the cases had previously required injections of parathyroid hormone, in addition to a high calcium intake, to prevent tetanic seizures, but when the phosphorus intake was reduced parathyroid hormone could be dispensed with. These workers noted that the urine passed during the period of low phosphorus intake contained little or no phosphate, suggesting that the reduction in the level of the serum-phosphorus was brought about possibly by the excretion of the excess phosphorus as calcium phosphate in the faeces. The beneficial effect of a reduced phosphate intake in chronic hypoparathyroidism has been confirmed by Freyberg, Grant, and Robb (1936).

In neither of the studies quoted above did the investigation of the calcium and phosphorus metabolism include a complete balance of these elements during the change from a normal to a low phosphorus intake. Observations on the absorption and excretion of calcium and phosphorus during this critical period might be expected to furnish data regarding the beneficial effect of a decreased phosphorus intake. We have therefore investigated fully the calcium and phosphorus metabolism in three patients suffering from parathyroid deficiency, first on a high calcium diet with a relatively high phosphorus intake, and then on a low phosphorus diet in which the calcium intake was maintained at the previous high level by appropriate supplements of calcium lactate. Since the calcium intake was kept constant throughout the experiment, it is obvious that any change in the blood levels and in the balance of calcium and phosphorus was due to the reduction of the phosphate intake. Three subjects with normal parathyroid function and calcium metabolism were studied in the same way to serve as controls.

Methods

Throughout the experimental period the patients were treated in the Metabolic Ward of the Aberdeen Royal Infirmary, under the personal supervision of the Ward Sister. For each level of phosphate intake a constant weighed diet was given, and all cooking was done with distilled water. Distilled water was also given for drinking purposes, and tooth pastes or powders, which usually contain calcium carbonate, were prohibited. Urine and faeces were collected in three-day periods, 0.3 gm. of carmine being given in a capsule at the beginning of each period to allow of separation of the faeces. Duplicate diets were weighed out, and collected in three-day periods. For each level of phosphorus intake, such duplicate samples from three periods were analysed for calcium and phosphorus by the methods indicated below; the averages of the results of the three analyses were taken as representing the intake of calcium and phosphorus from the particular diet.

Blood. At the beginning of each three-day period a fasting sample of blood was collected in a syringe which had been sterilized in distilled water. Calcium was estimated in the serum by Clark and Collip's (1925) modification of the method of Kramer and Tisdall. The N/100 solution of potassium permanganate used in titrating the calcium oxalate was standardized on each occasion by the method described by Schwartz (1936). Inorganic phosphorus was determined in the serum by the method of King (1932).

Urine. Calcium was estimated by a modification of the method described for the analysis of calcium in foodstuffs in Technical Communication No. 9 of the Imperial Bureau of Animal Nutrition (1937). Total phosphorus was estimated in the urine by a modification of King's (1932) method for serum inorganic phosphorus, as used in the Courtauld Institute of Biochemistry, Middlesex Hospital, London, and obtained through the courtesy of Professor E. C. Dodds, Director of the Courtauld Institute.

Faeces and diet. Faeces and diet samples (the latter being previously minced) were dried at 100°C., and the dry residue weighed and powdered. Calcium was estimated by the method described in Technical Communication No. 9 of the Imperial Bureau of Animal Nutrition. Phosphorus was estimated by digesting 0.15 gm. samples of the dry, powdered residue with 2 c.c. of 60 per cent. perchloric acid on the sand-bath, and treating the colourless solution by the same method as for total phosphorus in the urine. All the analyses on diets, faeces, and urine were carried out in duplicate. Specimen diets are given in the Appendix (p. 231).

Results

Case 1. Female, aged 20 years. The patient had shown typical symptoms and signs of primary toxic goitre for two years before subtotal thyroidectomy was performed on February 2, 1937. On the day following this operation, carpopedal spasms appeared. These were treated by intravenous injections

of calcium gluconate and intramuscular injections of parathyroid hormone, and by the fifth day the symptoms of manifest tetany were relieved, although signs of latent tetany persisted, Chvostek's and Trousseau's signs being positive. The serum calcium at this point was 6.4 mg. per cent. The patient was given a high calcium diet which included $1\frac{1}{2}$ pints of milk daily. This diet was not weighed accurately, but contained approximately 1.5 gm. of calcium and 2.0 gm. of phosphorus daily. The addition of 30 gr. of calcium chloride four times daily increased the total daily calcium intake from food and medication to about 4.4 gm. As a result of these measures, the serum-calcium rose in four days to 7.5 mg. per cent. The patient was kept on this regime for three weeks, but the serum-calcium rose no further and the serum inorganic phosphorus level remained elevated, the values ranging between 6 and 7 mg. per cent. The signs of latent tetany persisted, and any untoward emotional upset, for example that occasioned by venepuncture, was enough to precipitate a severe carpopedal spasm. A month had then elapsed since operation, and it was concluded that the symptoms of tetany could not be attributed to any temporary damage to the parathyroid glands such as interference with their blood-supply, but must be due to permanent parathyroid deficiency. The patient was accordingly transferred to the Metabolic Research Ward, where the metabolic experiments described below were conducted. The first part of the experiment consisted in the administration of a diet containing 1.92 gm. of calcium and 1.66 gm. of phosphorus daily. To secure equilibrium on this intake, the balance experiment was not begun until the patient had been for three days on the diet.

As shown in Fig. 1, the serum-calcium fell slightly and the serum inorganic phosphorus rose after the first period of three days, due to the withdrawal of the calcium chloride; thereafter the serum-calcium and phosphorus remained constant at about 6.5 mg. per cent. and 7.1 mg. per cent. respectively. During the nine days on this regime (periods 1 to 3) the balance of calcium was strongly positive, with an average daily retention of 1.16 gm. The phosphorus balance was also markedly positive, with an average daily retention of 0.62 gm. In this case the positive balance was due to a decrease in the faecal rather than the urinary excretion of phosphorus, since the amount of phosphorus excreted in the urine was as great as in the normal subjects on an even higher phosphorus intake (cf. Fig. 4). This finding does not support the theory that the phosphorus retention of hypoparathyroidism is due to deficient excretion of phosphorus by the kidneys, either through a rise in the renal threshold for phosphorus (Ellsworth, 1932) or a lack of electrolytes or magnesium in the serum (Shelling, 1935).

The ratio of retention of calcium and phosphorus was 1.87:1, which corresponds closely with the calcium:phosphorus ratio of calcium phosphate (1.93:1), suggesting that the retained calcium and phosphorus were being deposited in the bones. Radiological examination of the skeleton at this time showed a well-marked generalized osteoporosis, which was attributed to the preceding thyrotoxicosis, since according to Hunter (1930) about

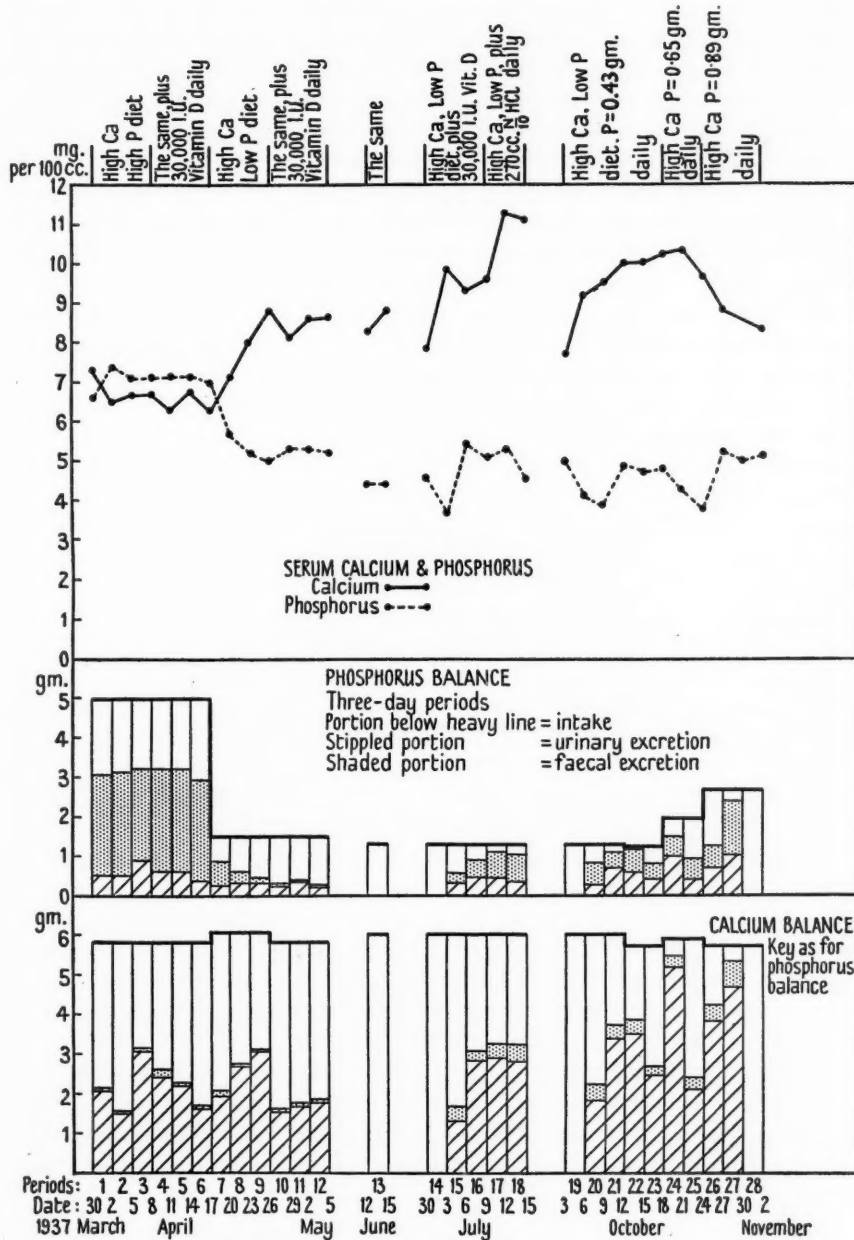


FIG. 1. Calcium and phosphorus metabolism during the treatment of a case of chronic hypoparathyroidism (Case 1).

50 per cent. of cases of toxic goitre exhibit demonstrable osteoporosis. The marked retention of calcium and phosphorus shown in the balance experiment was therefore considered to be due to deposition of lime salts in the bones as a result of the relief of the condition of hyperthyroidism, rather than to any effect of parathyroid deficiency, since neither of the other two parathyroprivic patients showed these marked retentions on a similar diet.

Additional therapy was then given in the form of vitamin D, in a dose of 30,000 international units daily, since many authors (Bauer, Marble, and Clafin, 1932; Boothby and Davis, 1936; Albright, Bloomberg, Drake, and Sulkowitch, 1938) have shown that vitamin D is capable of raising the serum-calcium in parathyroid deficiency. The addition of vitamin D in this dosage had no effect either on the levels of calcium or inorganic phosphorus in the serum, or on the retention of calcium and phosphorus, the average daily retentions of these elements in periods 4 to 6 being 1.17 gm. of calcium and 0.62 gm. of phosphorus, values identical with those of the preceding periods when no vitamin D was given. The criticism might be advanced that a period of nine days was too short a time to allow an effect of vitamin D to be demonstrated. We consider the failure of vitamin D to exert an action in this case to be due rather to insufficient dosage, since in Case 3, reported here, we obtained a rise in the serum-calcium level within three days of giving 45,000 international units of vitamin D daily.

At period 7 the diet was changed to a low phosphorus diet. In this case, the diet contained 0.162 gm. of calcium and 0.499 gm. of phosphorus daily. Sufficient calcium lactate was given to bring the calcium intake up to approximately 2 gm. daily. The salt was given as a 5 per cent. solution, the calcium content of which was estimated by the same method as that described for urinary calcium (1 c.c. aliquots of the solution being taken for analysis) and the daily dose measured out accurately. It was hoped that giving the salt in solution would facilitate absorption of the calcium. The response to this alteration in therapy was immediate. The serum-calcium increased within three days from 6.3 to 7.1 mg. per cent., and continued to rise until it reached a maximum level of 8.8 mg. per cent. in nine days. The serum-phosphorus showed a reciprocal fall, and decreased from 7.0 to 5.0 mg. per cent. in nine days. The average daily retention of calcium during periods 7 to 9 was 1.13 gm., almost the same as that on the high phosphorus diet, so that the rise in the serum-calcium level could not be attributed to an increased retention of calcium. The patient remained in positive phosphorus balance even on the low phosphorus intake. The average daily phosphorus retention was reduced from 0.62 to 0.29 gm. daily. A possible explanation for the improvement in the blood chemistry would be that phosphorus was being withdrawn from the body tissues and fluids to be laid down in the bones along with the retained calcium, with a consequent reduction in the serum-phosphorus, and a secondary increase in the serum-calcium.

After the serum-calcium had reached its maximal level at the end of nine days, vitamin D was given in a dose of 30,000 international units daily

during periods 10 to 12, the diet and calcium lactate being unaltered. No further rise in the serum-calcium was produced, but the daily calcium retention was increased from 1.13 to 1.34 gm. The serum-phosphorus level showed a slight tendency to rise, and the daily phosphorus retention was increased from 0.29 to 0.39 gm. It is interesting to note that throughout the whole period of observation only traces of calcium were present in the urine; the serum-calcium level never rose significantly above 8.5 mg. per cent., the value accepted by Aub, Albright, Bauer, and Rossmeisl (1932) as representing the renal threshold for calcium excretion. Also, the urinary excretion of phosphorus showed a progressive decrease on the low phosphorus intake until only traces were present in the urine.

The signs of latent tetany disappeared when the serum-calcium level rose above 8.0 mg. per cent., and the patient then felt perfectly well. She was discharged on May 8, 1937, with instructions to continue taking the low phosphorus diet and sufficient calcium lactate to maintain her calcium intake at 2 gm. daily. The patient reported on June 12, 1937, on which date her serum-calcium was 8.3 mg. per cent., and three days later, 8.8 mg. per cent. The serum-phosphorus had fallen to a normal level of 4.4 mg. per cent. She was next seen on June 30, 1937, when she admitted to having been irregular in taking calcium lactate. Her serum-calcium was found to have fallen to 7.9 mg. per cent., and her serum-phosphorus was 4.6 mg. per cent. She was at once placed on the low phosphorus diet plus calcium lactate solution, and 30,000 international units of vitamin D were given daily in view of the previous finding that this addition to the regime of a low phosphorus diet plus calcium lactate caused an increased calcium retention. After three days, a further balance experiment was begun on July 3, 1937 (period 15). Again the response to treatment was rapid. Within three days the serum-calcium had risen from 7.9 to 9.9 mg. per cent., and the serum-phosphorus had fallen from 4.6 to 3.7 mg. per cent. Thereafter the serum-calcium fell slightly, but remained above the lower limit of normal, while the serum-phosphorus rose in a remarkable fashion to over 5 mg. per cent. It is difficult to attribute this rise to phosphorus retention as a result of vitamin D administration, as suggested by Shelling and Goodman (1934) in their case of parathyroid deficiency receiving vitamin D, since the phosphorus retention was considerably less than that found when the patient was on a similar regime at the end of the first balance experiment. The calcium balance was still markedly positive. The urinary excretion of calcium was, however, then considerably greater than on her previous admission, confirming Aub's finding that a serum-calcium of about 8.5 mg. per cent. represents a critical level for the excretion of calcium by the kidneys.

During the periods 17 to 18 the patient was given in addition 270 c.c. of N/10 hydrochloric acid daily. The serum-calcium rose suddenly from 9.6 to 11.3 mg. per cent. at the end of the first three days, and was maintained at this level after a further three days. The serum-phosphorus fell during the six days of hydrochloric acid administration from 5.1 to 4.5 mg. per

cent. The alkali reserve of the blood showed a slight fall during the six days when acid was given from 63 volumes to 58.5 volumes per cent. It is well recognized that the administration of acid or acidifying salts in parathyroid deficiency will raise the serum-calcium from hypocalcaemic towards normal levels. In this instance, where the serum-calcium was already normal, the administration of acid produced a rise in serum-calcium to a value at, or just above, the upper limit of normal, an effect similar to that produced by the administration of acidifying salts to normal subjects, as described by Stewart and Haldane (1924). The calcium balance was still strongly positive, although the urinary excretion of calcium increased slightly. The results suggest that, in the doses given, acid therapy in parathyroid deficiency, as in the normal, increases the absorption of calcium from the intestine and causes no depletion of the skeletal stores of this element, provided the calcium intake is adequate.

The patient was next seen on October 3, 1937. As before, she admitted to having been irregular in taking the prescribed amount of calcium lactate. Her serum-calcium was 7.7 mg. per cent. and her serum-phosphorus 5.0 mg. per cent. She felt well, however, and there were no signs of latent tetany. She was placed on the low-phosphorus diet with calcium lactate sufficient to give the usual daily intake of 2 gm. of calcium. Within three days, the serum-calcium had risen to 9.2 mg. per cent. and the serum-phosphorus had fallen to 4.1 mg. per cent. By the end of the fifth three-day period the serum-calcium had become stabilized at a level just above 10.0 mg. per cent. A balance experiment during the last four periods of this regime (periods 20 to 23) showed that the average daily retention of calcium was then 0.91 gm. and that of phosphorus 0.09 gm., both values being lower than those obtained on a similar regime during periods 7 to 9.

To ascertain how far the phosphorus intake could be increased without producing a fall in the serum-calcium, the diet was accordingly changed to one yielding 0.65 gm. of phosphorus daily during periods 24 to 25, the calcium intake being kept constant at 2 gm. daily. At the end of the six days the serum-calcium had fallen slightly to 9.7 mg. per cent.; the serum-phosphorus fluctuated, but remained below 5 mg. per cent. A further increase in the daily phosphorus intake to 0.89 gm. at period 26 caused a deterioration in the blood chemistry. The serum-calcium fell first to 8.8, and then further to 8.3 mg. per cent., while the serum-phosphorus rose to a level of just over 5 mg. per cent. The increase in phosphorus intake caused a marked reduction in the retention of calcium, although the balance was still positive. The average daily retention of calcium during periods 24 to 27 was only 0.46 gm., while that of phosphorus had increased to 0.26 gm. daily. The ratio of retention of calcium and phosphorus was 1.77:1, indicating that more phosphorus was being retained than was required for deposition with calcium in the bones as calcium phosphate; the tendency of the serum-phosphorus to rise supports this finding. We believe that the fall in serum-calcium was dependent on this phosphorus retention.

From these results it was concluded that, in this patient, when the daily calcium intake was 2 gm., the maximal amount of phosphorus which could be taken daily without causing the serum-calcium to fall below a normal level lay between 0.5 and 0.65 gm. The patient was discharged on November 1, 1937, on the same low phosphorus diet with added calcium. She has reported on two subsequent occasions. The serum-calcium has remained within normal limits, although the serum-phosphorus on the last occasion was 5.3 mg. per cent. It should be noted that, in spite of the low protein content and relatively low caloric value of the low phosphorus diet, the patient's weight had only fallen from 9 st. 5 lb. on March 30, 1937, to 8 st. 11 lb. on October 16, 1937, and it has remained at about this level since.

The results of the balance experiments on this patient may be summarized :

1. The patient's chronic tetany was not ameliorated by a high calcium diet when this diet had also a high phosphorus content.

2. When the phosphorus content of the diet was reduced but the calcium intake remained high, there was an immediate trend of the serum-calcium and phosphorus levels towards normal values.

3. The rise in the serum-calcium could not be attributed to an increased retention of calcium, and the fall in the serum-phosphorus was not accompanied by any loss of phosphorus from the body.

4. The administration of hydrochloric acid in amounts of 270 c.c. of N/10 solution daily caused a rise in the serum-calcium to the upper limit of normal, but there was no significant decrease in the amount of calcium retained.

5. An increase in the phosphorus intake from 0.5 to 0.65 gm. daily caused the serum-calcium to fall to the lower limit of normal, while a further increase to 0.89 gm. daily caused a further fall in the serum-calcium to a definitely hypocalcaemic level.

Case 2. Female, aged 38 years. This is the second of the two cases of post-operative parathyroid deficiency (Mrs. B), whose treatment is described by Campbell (1935), and the following summary of her history up to 1930 is taken from his paper. The patient was operated on for exophthalmic goitre in August 1927, in India, and developed tetany five days later. Treatment with parathyroid hormone injections gave only partial relief. A year later she went through a normal pregnancy and fed the child herself, but severe tetany developed after six months' lactation, and the patient also suffered from a series of epileptiform convulsions with complete loss of consciousness. On admission to the Western Infirmary, Glasgow, in 1930, she had all the signs of tetany, and her serum-calcium was 5.5 mg. per cent. Rapid improvement followed treatment with a high calcium diet, acid, and calcium chloride, and she was discharged, free from symptoms, on a regime consisting of an ordinary diet plus one litre of milk, 50 c.c. of N/3 hydrochloric acid, and 90 gr. of calcium chloride daily. For two years the patient remained well, and in 1932 again went through a normal pregnancy and fed the child

herself. After two months' lactation, symptoms of tetany recurred and persisted for about six weeks.

The patient was in good health for the next three years, and a third child was born in 1935. After the birth of this child, she developed puerperal fever and 'kidney trouble', and since that time her general health was only fair. Attacks of tetany recurred at intervals of a few months, and since 1936 there was progressive dimness of vision due to bilateral cataract. In 1937 the patient became pregnant for the fourth time, but this pregnancy had to be interrupted owing to severe vaginal haemorrhage. Subsequently, mild attacks of tetany followed any undue fatigue and occasionally developed spontaneously without any obvious exciting factor. A gradual increase in weight occurred over the last few years.

On admission to the Royal Infirmary, Aberdeen, on May 11, 1938, physical examination revealed a moderate degree of obesity, but no thickening or dryness of the skin and no loss of hair from the head or eyebrows. The pulse-rate varied from 68 to 96 during the eight weeks she was in hospital. The blood-pressure was 130 systolic and 88 diastolic. The apex-beat was displaced slightly to the left, but otherwise examination of the heart, lungs, abdomen, and central nervous system was negative. There were no signs of latent tetany. The urine was pale and had a specific gravity of 1017. There was no albumin, and the deposit contained no casts or red-blood cells.

Special examinations: Radiological examination of the skeleton showed no abnormality of calcification. The basal metabolic rate was -20 and -27 per cent. on two examinations. The blood showed a slight degree of anaemia; the haemoglobin was 85 per cent. (Haldane), red-blood cells 4,570,000 per c.mm., white-blood cells 4,800 c.mm. The blood chemistry on admission was: serum-calcium 9.8 mg. per cent.; serum-phosphorus 5.3 mg. per cent.; total serum proteins 7.2 gm. per cent.; blood urea 54 mg. per cent. Renal functional tests showed a moderate impairment of kidney function. The urea clearance was 44 per cent. of normal, and a urea concentration test showed a maximum concentration in the urine of 1.75 gm. per cent. A fractional test meal showed that the histamine-fast achlorhydria noted by Campbell (1935) was still present. Ophthalmological examination by Dr. W. Clark Souter showed a considerable degree of myopic astigmatism and bilateral lens opacities, corresponding in nature to the cataract of parathyroid deficiency.

A balance experiment was commenced on May 13. As in Case 1, the patient was first given a high calcium, high phosphorus diet, yielding in this case 1.97 gm. of calcium and 2.03 gm. of phosphorus daily. It was hoped that the patient could be kept on this regime for several periods without any severe manifestations of tetany, in order that the transition from the high to the low phosphorus intake could be studied. By midnight of the first day on this regime, however, the patient developed all the symptoms of manifest tetany, with sweating, formication, slight pyrexia, blurring of vision and diplopia, and carpopedal spasm. An examination of the blood

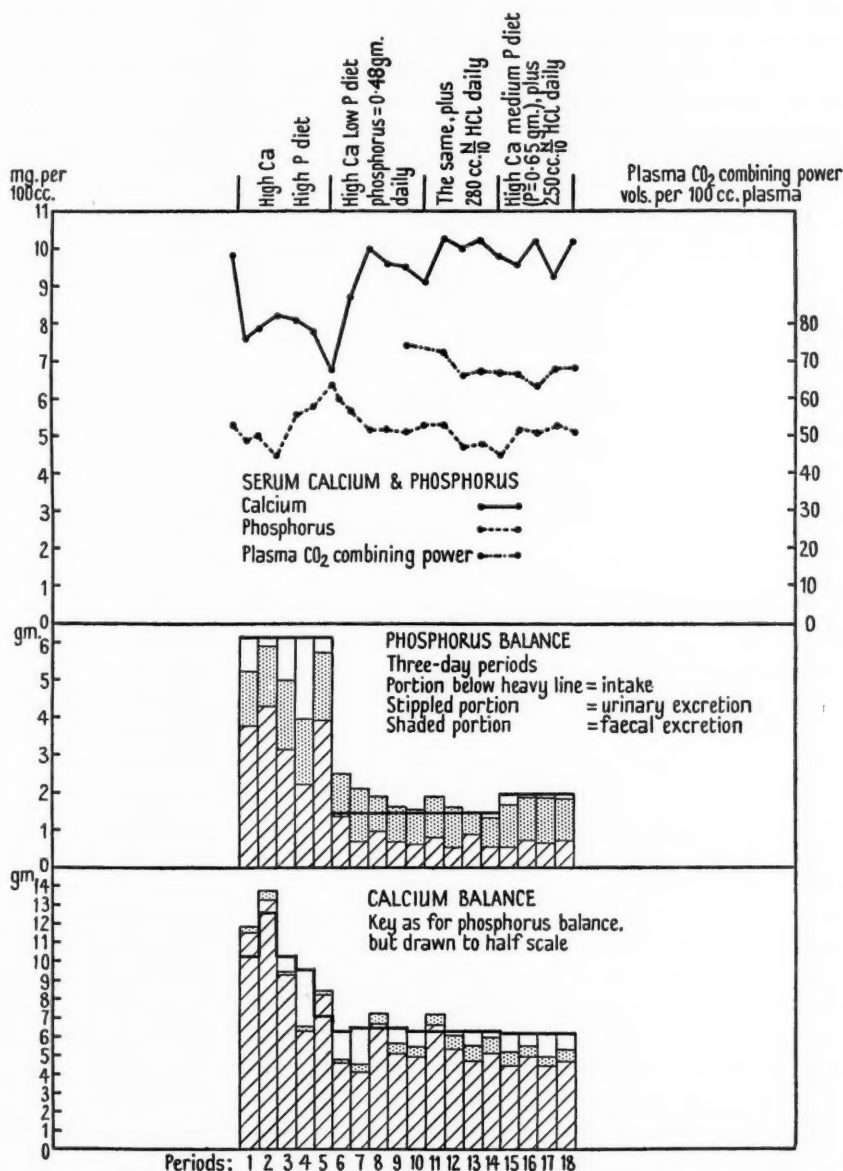


FIG. 2. Calcium and phosphorus metabolism during the treatment of a case of chronic hypoparathyroidism complicated by chronic renal disease (Case 2).

on the following morning showed that the serum-calcium had fallen from 9.8 to 7.6 mg. per cent. Accordingly, 5 per cent. calcium lactate solution was given by mouth to a total amount of 300 c.c. daily. The symptoms of manifest tetany passed off that evening, except for a slight degree of carpal

spasm, sufficient to prevent finer movements of the fingers. The Chvostek and Trousseau signs were strongly positive.

In the first three periods of such treatment, during which the daily calcium intake had been 3.38, 4.08, and 3.38 gm. respectively, the serum-calcium, after its initial fall to 7.6 mg. per cent., rose slightly to just over 8 mg. per cent. Latent tetany was present continuously, but no further attacks of manifest tetany occurred. In period 4 the calcium intake was reduced to 3.15 gm. daily, and in period 5 to 2.32 gm. daily. This caused a second fall in the serum-calcium to 6.7 mg. per cent., while the serum-phosphorus level showed a reciprocal rise to 6.4 mg. per cent. Apart from a slight attack of manifest tetany during period 5, relieved by taking 50 c.c. of the daily allowance of 5 per cent. calcium lactate solution, no untoward symptoms appeared. In considering the calcium and phosphorus balances during the five periods on the high phosphorus intake, it will be seen that there is a retention of phosphorus unrelated to the calcium balance. Actually, the calcium balance over these five periods was negative, the average daily loss being 0.11 gm., whereas there was an average daily retention of 0.31 gm. of phosphorus. As would be expected with the low serum-calcium level, practically all the calcium excretion was by way of the faeces, only traces appearing in the urine.

The phosphorus excretion is noteworthy in that the proportion of phosphorus excreted in the faeces is greater, and that in the urine less, than in normal subjects on a similar phosphorus intake, the ratio of faecal:urinary phosphorus in this case being 2.1:1, whereas the average ratio in the three normals is 0.8:1. In view of the fact that Cases 1 and 3, while on a high phosphorus intake, both excreted as much phosphorus in the urine as the normal subjects, the shift in the path of excretion of phosphorus from urine to faeces seen in this case cannot be attributed to the parathyroid deficiency. This alteration in the path of excretion of phosphorus may have been due to diminished absorption of phosphorus as a result of its precipitation as calcium phosphate in the intestine brought about by the high calcium intake. A similar shift was shown to occur in normal children by Telfer (1922) and Orr, Holt, Wilkins, and Boone (1924). Impairment of renal function may also have played a part, since in the cases of chronic nephritis in children studied by Boyd, Courtney, and MacLachlan (1926) the excretion of phosphorus in the faeces exceeded that of normal children on a comparable phosphorus intake. In two cases of renal rickets (unpublished results), where the calcium intake was normal, we have noted a similar shift in phosphorus excretion from urine to faeces.

At period 6 the patient was given a low phosphorus diet, yielding 0.48 gm. of phosphorus daily, with sufficient calcium lactate solution to give a total daily calcium intake of approximately 2 gm. As in Case 1, the response to this form of therapy was immediate and striking. The serum-calcium level rose rapidly, increasing from 6.7 to 8.7 mg. per cent. in the first three days, and reaching a normal level of 10.0 mg. per cent. within six days of the com-

mencement of treatment, after which there was a gradual fall over the next nine days to 9.1 mg. per cent. The serum-phosphorus showed a reciprocal fall, decreasing progressively from 6.4 to a constant level of just over 5 mg. per cent. Coincident with the return of the blood chemistry towards normal levels, there was an improvement in the clinical condition. It required a progressively longer period of compression of the arm with the sphygmomanometer cuff to elicit Trousseau's sign, which finally became negative five days after low phosphorus therapy had been instituted, at a time when the serum-calcium had risen to a point between 8.7 and 9.3 mg. per cent.

The balance of calcium and phosphorus during five periods on the low phosphorus intake (periods 6 to 10) shows a reversal of the conditions present when the phosphorus intake was high. The calcium balance became positive, with an average daily retention of 0.37 gm., while the phosphorus balance became negative, the average daily loss being 0.14 gm. As in Case 1, the urinary calcium excretion continued to be very low until the serum-calcium rose to a level above 8.7 mg. per cent., when a sudden increase occurred.

The effect on the blood chemistry of the change from a high to a low phosphorus intake is more easy to explain here than in Case 1, for it was associated with a retention of calcium and a loss of phosphorus from the body, conditions which would be expected to have the action observed on the levels of calcium and phosphorus in the serum. That the establishment of a negative phosphorus balance or an increase in calcium retention is not, however, essential for the favourable effect of a reduction in the phosphorus intake on the serum-calcium level is shown by the results obtained in Cases 1 and 3. The negative phosphorus balance in this case, on an intake which was adequate to maintain phosphorus equilibrium in the other two patients, may have been due to the relatively rapid weight-loss which occurred, the patient losing 10 lb. in weight during the five weeks following the commencement of the low phosphorus regime. Part of this loss in body weight may have been at the expense of protein, since the low phosphorus diet is admittedly low in protein. If such a breakdown in body protein occurred, a certain amount of phosphorus would have been liberated from it to appear in the excreta. Also, the body weights in Cases 1 and 3 were considerably less than that of the patient under consideration, and it is not improbable that the minimal intake of phosphorus necessary to maintain equilibrium will vary with the body weight of the individual. It should further be noted that the total amount of phosphorus retained during the five periods of high phosphorus intake was 4.62 gm., while the total amount lost during the first five periods of the low phosphorus intake was only 2.35 gm. The conversion of the negative calcium balance to a positive one by lowering the phosphorus intake is readily understandable when the disproportionately great phosphorus excretion in the faeces on the high phosphorus intake is recalled. This excess of phosphorus in the faeces must have caused the precipitation of a large amount of calcium in the intestine as the insoluble calcium phosphate, and so increased the calcium intake required to establish equilibrium.

At the end of period 9, the patient, who had felt perfectly well after the signs of latent tetany disappeared, began to complain of headache, nausea, and an unpleasant taste in the mouth. In view of the known alkalizing effect of calcium lactate, and the patient's impaired renal function, a provisional diagnosis of alkalosis was made. The finding of a carbon dioxide combining power of the plasma of 74 volumes per 100 c.c. confirmed the clinical impression that a mild alkalosis was present. Accordingly, beginning with period 11, the calcium lactate was given in N/10 hydrochloric acid instead of water. This gave an intake corresponding to 280 c.c. of N/10 hydrochloric acid daily, and resulted in a fall in the carbon dioxide combining power of the plasma, which reached the upper limit of normal within six days, and remained between 63 and 68 volumes per 100 c.c. throughout the remainder of the experiment. Coincident with this fall in the alkali reserve, the patient's symptoms disappeared. In describing the treatment of tetany, Shelling (1935) states that the use of hydrochloric acid as an adjuvant to calcium salts is contra-indicated in cases complicated by nephritis in view of the danger of the production of an uncompensated acidosis. From our experience with this patient, we feel that there is an equally great danger of producing an alkalosis in such cases by the administration of large doses of calcium lactate, and that any case of tetany complicated by nephritis receiving such treatment should have the carbon dioxide combining power of the plasma estimated at intervals, so that appropriate doses of acid can be given if any tendency to alkalosis occurs. With the institution of acid therapy there was, as in Case 1, a secondary rise in serum-calcium level from 9.1 to just over 10.0 mg. per cent., while the serum-phosphorus showed a further fall to a level of 4.5 mg. per cent. There was, however, a significant decrease in the calcium retained during the four periods in which acid was given (periods 11 to 14), the average daily retention being only 0.007 gm. It will be seen from the chart that the acid had the usual effect of increasing the excretion of calcium in the urine. The phosphorus balance was still negative, the average daily loss being 0.04 gm. It is difficult to reconcile the decrease in calcium retention when acid was given in this case with the results obtained in normal subjects by Zucker (1921) and in two other cases of tetany in which we have studied this question; we shall refer to this point again in connexion with the conditions present during the last periods of the experiments.

Although the negative phosphorus balance had become very slight, it was obviously desirable to adjust the diet so that the patient could maintain equilibrium. Accordingly the phosphorus intake was increased at period 15 to 0.65 gm. daily, while the calcium intake was maintained at the previous figure of 2 gm., and 250 c.c. of N/10 hydrochloric acid were given daily. On this regime, the serum-calcium was maintained at a normal level, although the serum-phosphorus rose again to just over 5 mg. per cent., the level obtaining before the acid therapy was instituted. The average daily calcium retention increased to 0.31 gm., almost the same value as that obtained on

the low phosphorus intake before acid was given. Although there was a slight decrease in the amount of calcium excreted in the urine, the improved retention was also due in part to a lowering of the amount of calcium excreted in the faeces. On the increased phosphorus intake, there was a positive phosphorus balance, with an average daily retention of 0.045 gm.

It seems unlikely that a reduction in the daily intake of N/10 hydrochloric acid of only 30 c.c. would have produced the marked increase in calcium retention observed, and we consider that this can be attributed rather to the fact that the patient was now in positive phosphorus balance. It would seem, therefore, as if a qualification must be added to our previous statement that the administration of acid to a patient with tetany will not affect the calcium balance adversely, in that the patient must also be receiving sufficient phosphorus to maintain a positive balance for this element. How far the impaired renal function present in this case affected the results, it is difficult to say.

The patient was discharged on July 6, 1938, with detailed instructions regarding diet, calcium, and acid. Since then she has reported that there have been two attacks of tetany; on both occasions, however, these could be related to fatigue and failure to keep to the diet prescribed.

Case 3. Female, aged 34 years. The patient had suffered from a swelling in the neck and symptoms suggesting toxic goitre for eight years. Recently the symptoms had become more pronounced and she had lost weight. On examination, she presented the signs of toxic goitre; her basal metabolic rate was +72 per cent. Subtotal thyroidectomy was carried out on July 15, 1937. Recovery from the operation was uneventful, and the patient was discharged in August 1937 relieved of symptoms. She was next seen in February 1938. She gave the history that for two months after discharge from hospital she had felt very well and had been putting on weight. In October 1937, however, she began to suffer from tingling sensations, and attacks of stiffness of the hands and feet, during which, from the patient's description, the hands assumed the typical position of carpal spasm. When they first started, the attacks occurred three or four times daily, but had become much less frequent. In the intervals the patient was able to do housework, but she had noticed that any task involving finer movements of the hands, such as knitting, was impossible.

Physical examination showed a moderate degree of hypertension, but otherwise no abnormality of heart, lungs, abdomen, or central nervous system. Trousseau's sign was positive; Chvostek's sign was negative; and no increased electrical excitability of the peripheral nerves or muscles could be demonstrated. Slit-lamp microscopy showed no lenticular opacities. The blood chemistry was: serum-calcium 6.2 mg. per cent., serum inorganic phosphorus 4.3 mg. per cent., total serum proteins 6.9 gm. per cent.

The patient was admitted to hospital on February 28, 1938, and the balance experiment shown in Fig. 3 was commenced on March 7, 1938. In this subject the experimental procedure was modified in two respects:

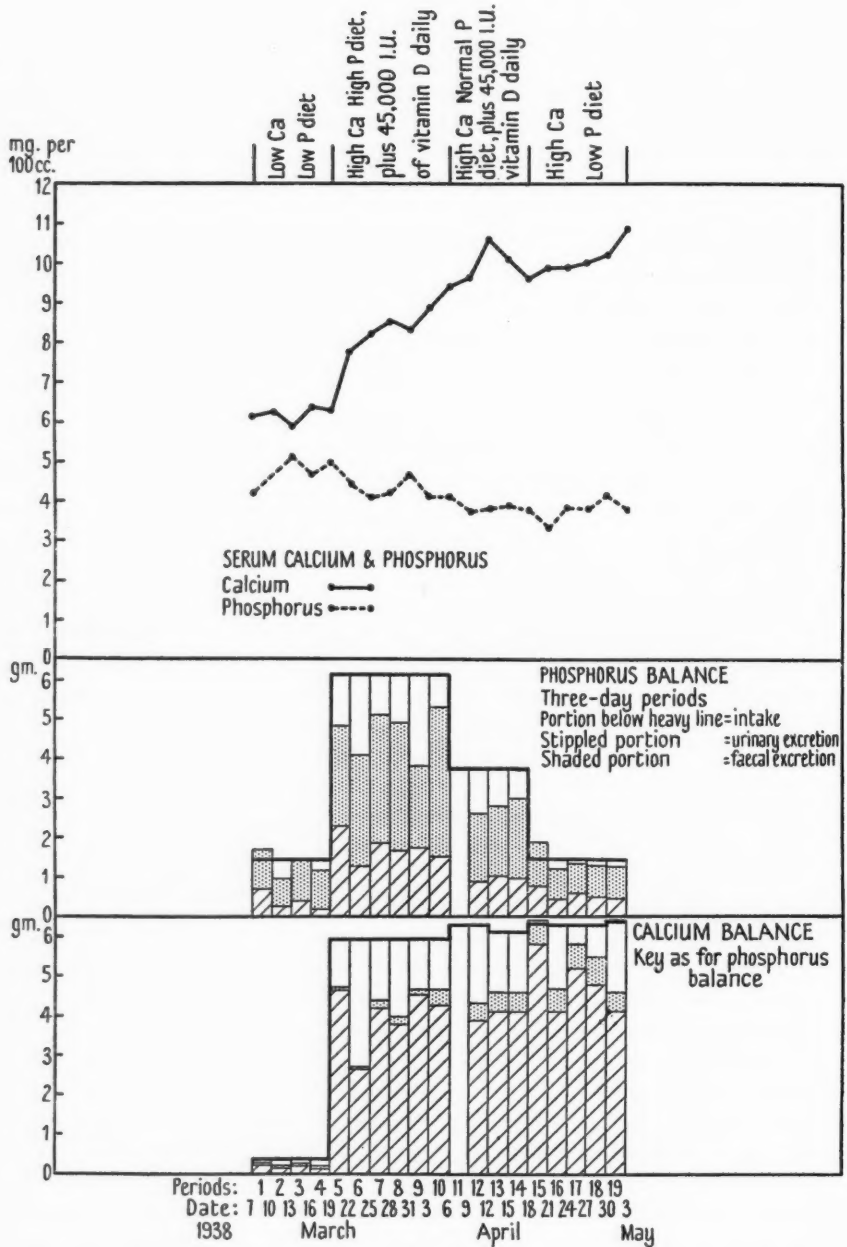


FIG. 3. Calcium and phosphorus metabolism during the treatment of a case of chronic hypoparathyroidism (Case 3).

(1) the patient was placed first on a low calcium diet to confirm the findings of Aub, Albright, Bauer, and Rossmeisl (1932) that subjects with parathyroid deficiency can maintain calcium equilibrium on an intake as low as 0.1 gm. of calcium daily. At this level of intake Bauer, Albright, and Aub (1929) showed that normal subjects were always in negative calcium balance, even when the demand for calcium was increased by pregnancy. After the patient had been for three days on the low calcium diet, which yielded 0.12 gm. of calcium and 0.48 gm. of phosphorus daily, collection of excreta was carried out over four periods (periods 1 to 4). During this time the serum-calcium remained approximately constant at a level of between 5.9 and 6.4 mg. per cent., while the serum-phosphorus rose from its initial level of 4.2 to 5.0 mg. per cent. During this period the patient was in positive balance for both calcium and phosphorus, the average daily retentions of both elements being 0.04 gm. daily. Even at this low level of phosphorus intake, the tendency to phosphorus retention in hypoparathyroidism is demonstrated, for, the calcium : phosphorus ratio of the retention being unity, more phosphorus was being retained than was required for deposition with the retained calcium in the bones as calcium phosphate. The rise in the serum-phosphorus level would suggest that this excess phosphorus was accumulating in the tissue fluids. (2) A high calcium, high phosphorus diet, yielding approximately 2 gm. of each element daily, was then given, at period 5. Our experience with Case 1 having shown that vitamin D in a dose of 30,000 international units daily had no effect on the hypocalcaemia of parathyroid deficiency, we resolved to determine the effect of increasing the dose to 45,000 international units daily.

The serum-calcium immediately began to rise, until it reached a normal level 18 days after the commencement of treatment. Trousseau's sign became negative when the serum-calcium reached a level of 7.8 mg. per cent. The serum-phosphorus level declined somewhat as the calcium level rose, falling from 5.0 to 4.1 mg. per cent. in 18 days. The calcium balance during periods 5 to 10 showed that there was an average retention of 0.58 gm. of calcium daily. As in the other two cases, the amount of calcium excreted in the urine, which had been very small while hypocalcaemia was present, became suddenly greater when the serum-calcium rose from 8.3 to 8.9 mg. per cent. There was also a positive phosphorus balance with an average daily retention of 0.47 gm. of phosphorus. Although the calcium : phosphorus ratio of retention was only 1.23 : 1, the phosphorus retained in excess of that required for deposition with calcium in the bones was not accumulating in the tissue fluids, since the serum-phosphorus level was falling during this period.

At period 11 the diet was changed to one with a normal phosphorus content of 1.23 gm. daily; the calcium intake was kept at 2 gm. by an appropriate daily supplement of 5 per cent. calcium lactate solution, and the same dose of vitamin D was continued. The serum-calcium, which was 9.4 mg. per cent. at the commencement of this period, rose to a maximum

of 10.6 mg. per cent. and then declined to its initial level; the serum-phosphorus declined from a level just over 4 to just under 4 mg. per cent. After an interval of three days, the balance of calcium and phosphorus on this new regime was investigated. The average daily retention of calcium during periods 12 to 14 was 0.55 gm., almost identical with that present during the preceding period of high phosphorus intake; the effect of vitamin D in promoting absorption of calcium from the intestine would therefore seem to be independent, within wide limits, of the phosphorus intake. The retention of phosphorus was then only 0.29 gm. daily. The calcium: phosphorus ratio of retention was 1.9:1, suggesting that all the retained phosphorus was being deposited as calcium phosphate in the bones. The experiment was concluded, as in Cases 1 and 2, by substituting at period 15 a low phosphorus diet for the previous high phosphorus one, the calcium intake being maintained at 2 gm. daily by means of calcium lactate solution. At the same time vitamin D administration was discontinued. With the change to the low phosphorus intake, the serum rose gradually from an initial level of 9.6 to 10.9 mg. per cent., while the serum-phosphorus level remained essentially unchanged.

The calcium balance during periods 15 to 19 remained positive, although the average daily retention fell to 0.32 gm. After a negative balance during the first period of low phosphorus intake, the patient remained just in phosphorus equilibrium, the average daily retention over periods 15 to 19 being only 0.005 gm. The rise in the serum-calcium level cannot be attributed, therefore, to any increase in the absorption of calcium, since this actually declined. A possible explanation might be that the decline in phosphorus retention almost to zero prevented deposition of any calcium phosphate in the bones. While a certain amount of the absorbed calcium was possibly deposited as calcium carbonate, the remainder, not being required by the body, would be carried by the blood to be excreted by the kidneys and intestine, and so cause an increase in the calcium level of the blood. Support is lent to this view by the fact that the calcium excretion in the urine increased when the phosphorus intake was reduced.

As in Cases 1 and 2, therefore, the levels of calcium and phosphorus in the blood of this patient could be kept normal by the simple expedient of reducing the phosphorus intake to about 0.5 gm. daily, along with sufficient calcium lactate to maintain a calcium intake of about 2 gm. Although the serum-calcium had been restored to normal before low phosphorus therapy was started, there is no reason to believe that it would not have been raised as quickly and effectively from hypocalcaemic levels by low phosphorus therapy as it was by the administration of vitamin D.

The patient was discharged on May 3, 1938, with instructions to continue the treatment at home. She has reported on three subsequent occasions, on each of which the serum-calcium and phosphorus have both been within normal limits. She is maintaining her weight, and feels perfectly well.

Conclusions and Summary

1. One of the most important points in the therapy of parathyroid deficiency appears to be the limitation of the intake of phosphorus in the

mg. per
100 cc.

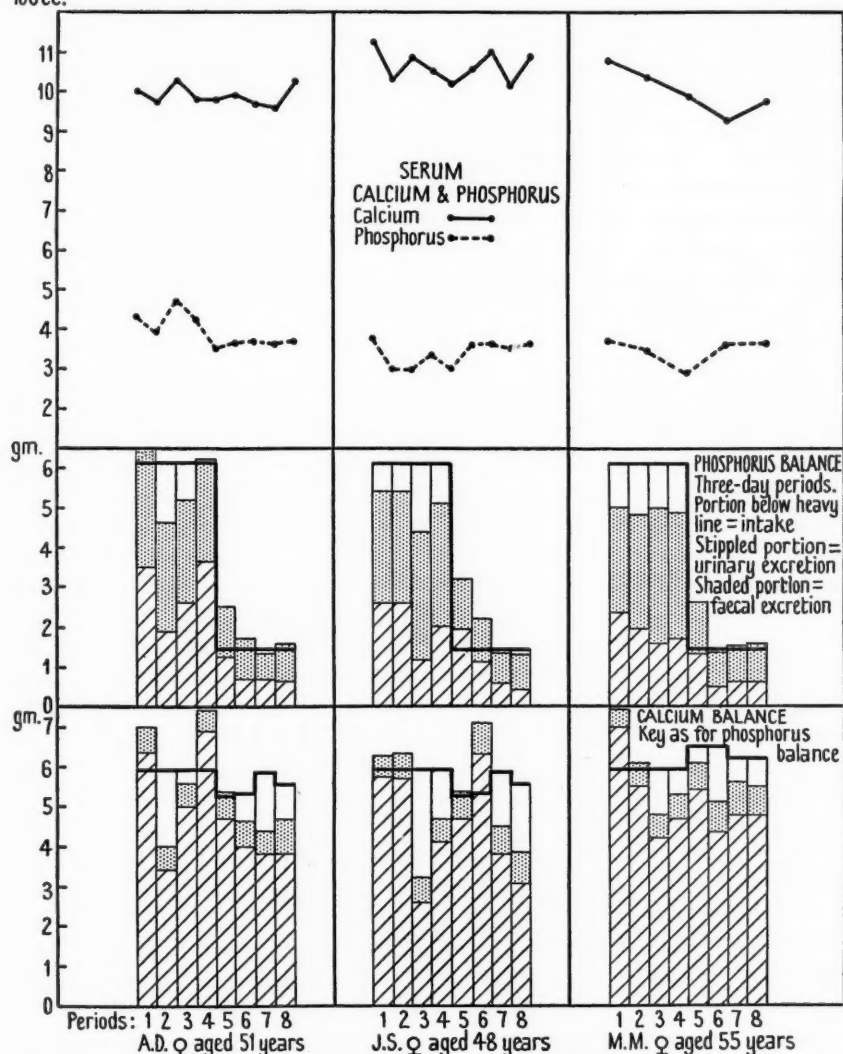


FIG. 4. Calcium and phosphorus metabolism of normal subjects during the change from a high calcium and phosphorus intake to a high calcium and low phosphorus intake.

diet. In three cases of post-operative parathyroid deficiency, the serum-calcium could be raised to, and maintained at, a normal level by the administration of a diet low in phosphorus together with large doses of

calcium lactate. The primary importance of this reduction in phosphorus intake is illustrated in Cases 1 and 2, where the same, or even a greater, calcium intake had no effect on the depressed serum-calcium level as long as the phosphorus intake remained high.

2. The suggested optimal level of phosphorus intake is from 0.5 to 0.65 gm. daily, depending on the body-weight of the individual. The small amount of calcium present in this diet is supplemented by sufficient calcium lactate (approximately 14 gm.) to give a calcium intake of 2 gm. daily. On such a regime the three patients investigated maintained normal levels of calcium and phosphorus in the serum and remained in equilibrium as regards the balance between the intake and excretion of calcium and phosphorus. No additional therapy in the form of vitamin D or acid was required, except in Case 2, which was a patient also suffering from chronic nephritis, to whom acid had to be given in amount sufficient to counteract the alkalizing effect of the calcium lactate.

3. The results of the balance experiments in these cases indicate that the improvement in the blood chemistry produced by a reduction of the phosphorus intake cannot be explained by an increased retention of calcium in the body or a loss of phosphorus from the body. The rise in serum-calcium seems rather to be secondary to the fall in serum-phosphorus, which in its turn appears to be the result of a diversion of phosphorus from the body-fluids to some other site in the body rather than of any loss of phosphorus from the body.

4. The amount of phosphorus excreted by the kidneys in the three cases of parathyroid deficiency on a high phosphorus intake was as great as in the three normal subjects on a similar phosphorus intake. Where the retention of phosphorus was greater than in normals (Cases 1 and 3), this was due to a decrease in the phosphorus of the faeces. Normal subjects have a negative phosphorus balance during the first twelve days after the phosphorus intake is reduced from 2 to 0.5 gm. daily, the calcium intake being 2 gm. daily throughout. Under similar conditions patients with parathyroid deficiency, unless there is complicating renal disease, remain in positive phosphorus balance, the excretion of phosphorus by the kidneys being less than in normal subjects on the reduced phosphorus intake.

5. In doses of up to 270 c.c. of N/10 hydrochloric acid daily, acid therapy does not adversely affect the calcium balance of patients with parathyroid deficiency, provided the calcium intake is adequate and sufficient phosphorus is being given to maintain phosphorus equilibrium.

6. The minimal dose of vitamin D necessary to raise the serum-calcium to a normal level in parathyroid deficiency appears to lie between 30,000 and 45,000 international units daily. The higher dose mentioned is effective even when the phosphorus intake is not reduced.

7. There is thus evidence of a decreased excretion of phosphorus by the kidneys in parathyroid deficiency only when the phosphorus intake is low. When the phosphorus intake is high the kidneys of patients with para-

thyroid deficiency are capable of excreting as much of the excess phosphorus as are those of normal subjects. This suggests that the retention of phosphorus found in parathyroid deficiency cannot be explained by any impairment of the ability of the kidneys to excrete phosphorus, since, if such were the cause of the retention, it would be expected that an increase in phosphorus intake would aggravate the defect.

We wish to thank Professor L. S. P. Davidson, Professor David Campbell, and Mr. G. Gordon Bruce, of the staff of Aberdeen Royal Infirmary, for permission to investigate Cases 1, 2, and 3 respectively. We are glad to acknowledge invaluable help from Sister Stephen of the Metabolic Ward and Sister Thomson of the Dietetic Department in the construction and preparation of the diets and in the careful collection of material.

This work was done during the tenure of a Beit Memorial Research Fellowship by one author (I. A. A.).

APPENDIX

1. High-calcium, high-phosphorus diet

Protein 86 gm. Fat 103 gm. Carbohydrate 203 gm. Calories 2083; Calcium 1.92 gm. Phosphorus 1.66 gm.

Breakfast:

1 egg
White bread 45 gm.
Butter from ration
Tea with milk from ration

Mid-forenoon:

Glass of milk

Lunch:

Lean meat 60 gm.
Potato 50 gm.
Curds with milk from ration
Cream 30 gm.
Apple 100 gm.

Afternoon:

Glass of milk

Tea:

White bread 45 gm.
Tomato 100 gm.
Butter from ration
Tea with milk from ration

Supper:

White bread 30 gm.
Finish butter ration
Finish milk ration

Daily rations:

Butter 30 gm.
Milk 1,500 gm.
20 per cent. cream 30 gm.

2. Low-calcium, low-phosphorus diet

(Supplemented with 250 c.c. of 5 per cent. calcium lactate solution.)

Protein 51 gm. Fat 82 gm. Carbohydrate 199 gm. Calories 1738; Calcium 0.14 gm. Phosphorus 0.48 gm.

Breakfast:

Orange juice 60 gm.
White bread 30 gm.
Bacon 45 gm.
Butter from ration
Tea with cream from ration

Mid-forenoon:

Orange juice 60 gm.

Lunch:

Lean meat 60 gm.
Potato 90 gm.
Apple 90 gm.
White bread 15 gm.

Tea:

White fish 60 gm.
White bread 45 gm.
Tea with cream from ration

Supper:

White bread 30 gm.
Banana 90 gm.

Daily rations:

Butter 45 gm.
Cream 45 gm.
Sugar 50 gm.
Syrup 30 gm.

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THE DIFFERENTIAL DIAGNOSIS OF FORMS OF
BASOPHILISM (CUSHING'S SYNDROME), PARTICULARLY
BY THE ESTIMATION OF URINARY ANDROGENS¹

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With Plates 14 to 17

Introduction

THE syndrome described by Cushing in 1932, and known by his name, was ascribed by him to the presence of a tumour of the basophil cells of the anterior part of the pituitary gland. It is now known, however, that precisely the same clinical syndrome may occur in association with tumours of the adrenal cortex or, very rarely, of the thymus, or without an associated tumour in any of these organs. In all these circumstances, however, the basophil pituitary cells show the characteristic hyaline change (Crooke, 1935) which is now regarded as the common pathological denominator in all forms of basophilism.

Since marked improvement has followed the surgical removal of adrenal cortical tumours, their early recognition is obviously desirable. It has been claimed that it is possible to distinguish the forms of basophilism associated with an adrenal tumour from other forms of basophilism on clinical grounds alone, but this has not been our experience. In certain cases the presence of an adrenal tumour can be recognized directly by palpation or by X-ray photography after perirenal insufflation of air. These direct methods may, however, give negative or equivocal results, and we now bring forward evidence that differentiation of the adrenal cortical group may be made by estimating the greatly increased excretion of a urinary product of abnormal endocrine activity—the urinary androgens.

In the work now described we have applied the hypothesis that the level of urinary excretion of androgens, or of compounds closely allied to them, is an index of adrenal cortical activity rather than of gonadal activity. Since these compounds may be estimated biologically, and a certain class of them, the 17-ketosteroids (i.e. steroid compounds such as androsterone or *trans*-dehydroandrosterone, which have a ketonic group in position 17) can be rapidly estimated colorimetrically, there is available a method which might allow a decision to be made as to the presence or absence of a tumour

¹ Received February 24, 1939.

according to whether the level of excretion is excessive or within normal limits.

In this paper four cases of basophilism are reported in which clinical and post-mortem data recorded by one of the authors (A. C. C.) at the London Hospital have been correlated with laboratory investigations by the other (R. K. C.) at the National Institute for Medical Research. The results afford empirical support for the usefulness of a chemical examination of the urinary androgen excretion as a test for the presence of an adrenal cortical tumour in clinical basophilism.

Case Reports

Case 1 (adrenal tumour). A single man, aged 25 years, was admitted to the London Hospital under Professor Ellis on January 30, 1938. Four years before admission he had begun to have dull frontal and occipital headaches, worse in hot and wet weather. Eighteen months before admission he had noticed that he was rapidly becoming obese; his weight increased from 10½ to 13 st. He noticed that the obesity started at the back of his neck, spreading to the face and thence to the trunk, but sparing the limbs. He also noticed that his face was becoming excessively red. Subsequently, purplish streaks began to appear in his groins and more recently on the folds of his axillae. He also noticed that he was getting taller. (He said that a year previously he had been the same height as his brother, that is, 5 ft. 10 in.; his actual height on admission to the London Hospital was 6 ft.) He felt lazy, was very easily fatigued, and had lost several jobs on this account. His appetite was good and his bowels regular. There was no alteration in the growth of hair; he shaved on alternate days. There was nothing noteworthy in his previous or family history. A diagnosis of basophilism had been made some months before admission, and he had received an intensive course of deep X-ray therapy at the Hull Royal Infirmary, directed to the pituitary fossa. On admission to the London Hospital he weighed 13 st. 11 lb. His appearance is shown in the photographs (Plate 14, Figs. 2 and 3). There was marked obesity of the face and neck with a pad of fat over the lower cervical vertebrae. The obesity of the trunk was less marked, and the limbs were normal. Long purple striae were present on the upper anterior and lateral aspects of both thighs. Similar transverse striae were present in the lumbar region, a few smaller longitudinal striae on the medial aspect of both knees, and numerous broad purple striae on the anterior and posterior axillary folds. His face was red. The distribution of hair on the face and trunk was normal. There was marked acne vulgaris on the back, less on the front of his chest, and none on his face. There was a moderate kyphosis in the upper dorsal and cervical regions. There was pitting oedema of the feet, extending half-way up the shins. The visual fields and fundi were normal, and there were no abnormal physical signs in the central nervous system. The pulse-rate varied between 74 and 84. The heart was normal. The blood-pressure was 140/100 mm. of Hg on admission, and on the following day 160/115. Subsequent measurements never exceeded 125/95. It had been recorded by the Neuro-Surgical Department as 160/115 in November 1937. The lungs were normal. The abdomen was obese and relaxed with difficulty, but there was no tenderness and nothing abnormal palpable. There was no albumin in the

urine, and renal efficiency tests were normal. There was no glycosuria, and sugar tolerance tests were normal. A blood count showed 5,800,000 red-blood cells per c.mm., and a haemoglobin of 120 per cent. There were 14,600 white cells per c.mm. with a normal differential count, except for the occurrence of 15.5 per cent. of large hyaline cells and 1.5 per cent. neutrophilic myelocytes. There were two normoblasts seen in counting 200 white cells. The Wassermann reaction in the blood was negative. The serum-calcium and phosphatase, the plasma-phosphorus, and the calcium balance were normal. The plasma protein was 5.9 gm. per 100 c.c. The blood-cholesterol and the plasma-chloride were normal. The basal metabolic rate was 80 per cent. of normal. A lumbar puncture showed a resting pressure of 165 mm. of C.S.F.; there was no block. The cerebrospinal fluid was normal. X-ray films of the skull showed a rather small sella turcica, but were otherwise normal. There was no X-ray evidence of a thymic tumour, and the lungs were normal. X-rays of the epiphyses at the lower end of the left radius and ulna, lower end of the left femur, and upper end of the left tibia and fibula showed normal union.

The high level of excretion of androgenic substances in the urine suggested the presence of an adrenal cortical tumour. An X-ray examination was made by the method of Cahill (1935). An insufflation of 250 c.c. of air was made into the perirenal tissue on both sides, and X-ray films were taken 18 and 24 hours afterwards. A tumour mass lying above the left kidney was outlined (Plate 15, Fig. 5). On March 14, 1938, the tumour was removed by Mr. V. W. Dix, using a lumbar approach. The whole tumour was covered by vascular fat, and was a partially encapsulated friable mass which bled freely and had to be removed in pieces. After removal the fragments of tumour together measured $16 \times 9 \times 6$ cm. On histological investigation it was found to be a polygonal and polymorphic, occasionally giant or multinucleate giant-celled, solid carcinoma of the adrenal cortex. A portion of the left adrenal gland was found which had been removed with the tumour. It was greatly atrophied and measured 0.15 cm. thick. Histological examination showed simple atrophy of the cortex with fibrosis of the zona reticularis.

His post-operative course was stormy. In addition to a massive collapse of the lower lobe of the left lung, he developed tachycardia, increased oedema, anaemia, and extensive peripheral neuritis. The pulse-rate was 160 to 190, the haemoglobin 46 per cent., and there was pain, marked weakness, and anaesthesia and analgesia of both upper and lower extremities with complete loss of deep reflexes. For two days after operation he was given 5 c.c. of cortical extract (Upjohn) 6-hourly, and saline intravenously and orally. This treatment was discontinued when the above-mentioned symptoms of peripheral neuritis developed on the third day after operation. It was thought that the association of acute polyneuritis, unexplained oedema, and severe unexplained tachycardia might be due to vitamin B deficiency, and he was treated with daily injections of 10 mg. of Benerva. Recovery was very slow, and was delayed by an attack of acute pericarditis four weeks after the operation. He was unstable mentally and occasionally disorientated. He was discharged to his home on May 15, nine weeks after operation, still with tachycardia, oedema, and severe peripheral neuritis.

He was readmitted on September 4, 1938. He then weighed 9 st. 11 lb. 11 oz., his height was recorded as 6 ft. 1 in., an inch more than on his first admission. His general appearance was strikingly altered (Plate 14, Fig. 4) and approached that seen in photographs taken before the onset of his illness.

The characteristic obesity, the bright red coloration of the face, and the seborrhoea of the chest had disappeared. The striae were as numerous as before, but were of a pale greyish-mauve colour and much less conspicuous. A few small new striae had appeared on the inner side of the knees. The blood-pressure was 118/85. There was still some weakness and wasting of both upper and lower extremities affecting the peripheral more than the proximal muscles. There was no disturbance of sensation and the deep reflexes were all present. There was a flexion contracture of the right knee. The haemoglobin was 72 per cent. The blood-urea, blood-cholesterol, plasma-phosphorus, plasma-chloride, and plasma-protein were normal, as were also a sugar tolerance test and the basal metabolic rate. There was marked improvement in hospital and he was discharged on October 1, 1938, feeling and looking well and able to walk without assistance.

Case 2 (adrenal tumour). A girl, aged 6 years, was first admitted to the London Hospital under Dr. Tallerman on July 25, 1936, on account of swelling of the abdomen of two weeks' duration. Pubic hair had been noticed for a month and nocturnal enuresis for six weeks before admission. On examination she weighed 3 st. 1 lb. 8 oz. In appearance (Plate 16, Fig. 6) she was a full-coloured, well-covered, healthy-looking child. The breasts were not enlarged, and a little dark pubic hair was present, but there was none on the face or in the axillae. There were no striae. The heart was not enlarged. The blood-pressure was 150/120 mm. of Hg. Expansion of the lungs was poor and the breath-sounds were diminished at the left base. The abdomen was distended by a large hard movable mass situated in the left loin and extending in front almost to the midline. There was a cloud of albumin in the urine, which was otherwise normal. The blood-urea was 0.027 gm. per 100 c.c. A sugar tolerance test was normal. A blood-count showed 4,200,000 red cells per c.mm., with a haemoglobin of 63 per cent., and a normal white count. During her stay in hospital she became more obese and her weight increased to 3 st. 8 lb. 3 oz. Her face became more coarse, and acne vulgaris appeared. Her skin became darker and hair appeared on her upper lip. The abdominal mass increased in size. It was decided that the tumour was too large for surgical removal, and she was discharged on September 3, 1936.

She was readmitted for further investigation on November 3, 1936. She then complained of occasional morning headaches and occasional left-sided abdominal pain. She weighed 4 st. 7 lb. She was definitely more muscular than other children of the same age in the ward. Obesity of the face, neck, and abdomen was marked, and there was a pad of fat over the lower cervical vertebrae. The limbs were normal. Acne vulgaris on the face was more marked. There was an increase of downy hair all over the body. There were no striae. The clitoris and labia majora were considered to be enlarged. The heart was slightly enlarged, the apex-beat in the fifth space $\frac{1}{2}$ in. external to the mid-clavicular line. The aortic second sound was accentuated. The systolic blood-pressure varied between 150 and 180 and the diastolic between 100 and 145 mm. of Hg. The condition of the lungs was unchanged. The abdominal mass was larger and the liver edge, firm and regular, was palpable 1 in. below the costal margin. There was up to a 1/10th volume of albumin in the urine, but renal efficiency tests were normal. There was never any glycosuria. On March 12, 1937, a blood-count showed 3,600,000 red cells per c.mm., with a haemoglobin of 46 per cent. There were 8,000 white cells per c.mm., of which 83 per cent. were polymorphonuclear neutrophils. Three normoblasts and one megaloblast were seen in counting 200 white

cells. There was no evidence of osteoporosis, and the epiphyses appeared to be united normally for a child of her age.

The patient's disorder continued to progress and she developed ascites. Purplish striae appeared on the lower part of her abdomen and down the anterior aspects of her thighs, and increased steadily in size and number. The appearance is shown in Plate 16, Fig. 7. Her weight increased to 5 st. 7 lb. 12 oz. before death. On April 14, 1937, she had an attack of acute heart-failure and died suddenly. At autopsy a large tumour measuring $28 \times 27 \times 14$ cm. was found replacing the left adrenal gland. The tumour was invading the adjacent surface of the left kidney. The lumbar and coeliac glands and one gland in the posterior mediastinum were infiltrated with the growth and there were a few small scattered nodules of secondary deposit in the liver. On histological examination the tumour consisted of a polygonal, polymorphic, frequently mononucleate or multinucleate giant-celled carcinoma of adrenal cortex. No tumour was found on examination of serial sections of the anterior lobe of the pituitary gland, but many of the basophil cells showed the characteristic hyaline change (Crooke, 1935).

Case 3 (absence of adrenal tumour). A girl, aged 12 years, was first admitted to the London Hospital under Dr. Maitland Jones on July 20, 1937. Her school medical reports showed that she had always been under weight, and a report dated July 7, 1936, stated that she was so poorly nourished, pale, and generally undersized, that she was sent away for a month's holiday. Three months later obesity was noted in her school report. Her mother said that her face changed in appearance and became bloated, and hair began to appear on her upper lip, on the back of her neck, and in the pubic region, and her eyebrows became thicker. She complained of occasional headache, chiefly over the left eye. On admission to hospital she measured 4 ft. in height and weighed 5 st. 4 oz. There was marked obesity of the face, chest, and abdomen. There was a large pad of fat on the back of the neck above the scapulae. The arms and legs were normal. There was a moderate amount of hair on the upper lip, on the shoulders, and in the pubic region. Her eyebrows were dark and bushy. The labia majora were considered to be large for her age. The heart was not enlarged, but the systolic blood-pressure varied between 115 and 140 and the diastolic between 85 and 110 mm. of Hg. The abdomen was obese and the liver edge was just palpable, but no other abdominal mass could be felt. There were no abnormal physical signs in the lungs or central nervous system. There was a cloud of albumin in the urine, but renal efficiency tests were normal. There was no glycosuria. X-ray examination of the skull, hands, and feet showed no abnormality, and radiological examination after perirenal insufflation failed to reveal an adrenal tumour. The patient was sent home.

She was readmitted to hospital on August 12, 1938. Her mother stated that since discharge she had remained about the same. She refused to eat properly on account of her obesity, or play with other children because they laughed at her ungainly shape, so that she stayed at home all the time. Frontal headaches had been increasing in intensity and frequency. For the last nine to twelve months she had had attacks of pain 'like a needle' starting in the small of the back and radiating round both sides to the iliac and hypogastric regions. The attacks lasted about five minutes at a time. On examination she measured 3 ft. 11 in. and weighed 4 st. 6 lb. 12 oz. Her general appearance (Plate 17, Fig. 8) had not changed. Her cheeks were ruddy and there was one small stria on the upper anterior aspect of the

right thigh. Cardioscopy showed that left ventricular hypertrophy had taken place. The systolic blood-pressure varied from 140 to 155 and the diastolic from 125 to 140 mm. of Hg. The haemoglobin was 85 per cent. and the leucocytes 14,840 per c.mm. A sugar tolerance test showed a fasting level of 0.13 gm. per 100 c.c., rising half an hour after 50 gm. of glucose to 0.24 gm. per 100 c.c., then falling rapidly to normal. X-ray examination showed a normal sella turcica. Radiological examination after perirenal insufflation of air showed a normal right adrenal gland, but the left adrenal could not be identified. An exploratory laparotomy was made by Mr. Allen Perry on September 16, 1938. There was no tumour in either adrenal gland.

Case 4 (absence of adrenal tumour). A married woman, aged 33 years, was first admitted to the London Hospital under Professor Ellis on October 23, 1935. Her catamenia had always been fairly regular until the first pregnancy, which terminated with a normal labour in October 1932. Her periods returned the following month and were regular until March 1933, when they ceased altogether except for a single period in August 1934. She remained well otherwise until March 1934, when she noticed that she was getting obese. Her weight which was normally between 10 and 10½ st. increased to 13 st. She noticed that her face was becoming dark red in colour and that the striae gravidarum which had been pale were becoming dark red. For some time before admission to hospital her eyes had been getting more prominent. There was a gradual onset of morning headaches. She was getting weak, easily tired, and irritable. She lost one stone in weight by dieting, but her symptoms became progressively worse. Her weight on admission was 12 st. 2 lb. 3 oz. There was marked obesity of the face and neck, with prominent pads of fat over the lower cervical vertebrae and over both clavicles. There was marked obesity of the abdomen, but the buttocks and limbs were not affected. The skin of the face was bright red with considerable underlying brown pigmentation, and there was similar brown pigmentation of the arms and legs. There was slight cyanosis of the lips and a purplish discoloration of the skin of both thighs, particularly above the knees. There were widespread purple striae on the abdominal wall, and pityriasis rosea on the trunk. There was a definitely abnormal amount of hair on the upper lip, but the distribution of pubic hair was normal. The eyes were prominent, but the thyroid was not enlarged; the breasts were normal. There was kyphosis, most marked in the upper dorsal region. The fundi were normal except for one small patch of white exudate below the right disc. Cardioscopy showed slight hypertrophy of the left ventricle with 'uncoiling' of the aorta. The blood-pressure was 200/120 mm. of Hg. There were no abnormal physical signs on examination of the central nervous system, heart, lungs, or abdomen. The visual fields were full. The urine contained a trace of albumin, but renal efficiency tests were normal. There was no glycosuria and a sugar tolerance test was normal. A blood-count on admission showed 5,630,000 red cells per c.mm., with a haemoglobin of 108 per cent., and a normal white cell count. X-ray films of the skull showed a normal sella turcica. There was no X-ray evidence of osteoporosis of the spine. She was treated with a diet of 1,100 calories and lost one stone in weight, but she felt so ill on this diet that it had to be discontinued, and she was discharged to her home.

She was readmitted to hospital on April 20, 1936. Her symptoms were unchanged, except that for the previous two months she had noticed that she bruised very easily. She weighed 11 st. 9 lb. 7 oz., and the general appearance was the same. The systolic blood-pressure varied between 170

and 215 and the diastolic between 110 and 145 mm. Hg. There was pitting oedema of the feet. The central nervous system was normal, but there was papilloedema of the right disc, and a small area of white exudate beneath it, and early papilloedema of the left disc. There were no abnormal physical signs in the lungs or abdomen. The urine constantly contained albumin at this time, varying in amount from 1/3 volume to a cloud. Renal efficiency tests gave figures still within normal limits. There was no glycosuria, and sugar tolerance tests were normal. The blood-count was similar to that on her first admission, and the basal metabolic rate was 69 per cent of normal. She was given 5 mg. of oestradiol daily for ten days. Eight days after the last injection there was a short and scanty menstrual period; there was no other change in her condition. She was discharged home after nine weeks in hospital.

She was readmitted on September 21, 1936, feeling worse. She was short of breath on exertion and had a sensation of fullness in her head. Six weeks before readmission she had had an attack of sharp pain with tenderness on pressure under the right arm, which was made worse by movement and by deep breathing. She also had had an attack of pain in the fingers of the left hand running up the forearm, and a similar attack in the right foot. She had frequency of micturition, two to three times by day and three to four times by night, but no pain or difficulty. There had been no further menstrual loss. On examination she weighed 11 st. 4 lb. 3 oz. Her appearance then is shown in the photograph (Plate 17, Fig. 9). She was slightly cyanosed. The brown pigmentation of the skin was deeper in colour and widespread over the whole body. The pityriasis rosea on the trunk was worse. Moderate exophthalmos had developed. She was slightly orthopnoeic, there was moderate pitting oedema of the feet, and slight oedema of the shins. Scattered petechiae and small subcutaneous ecchymoses appeared on her arm after compression with a sphygmomanometer cuff. The peripheral arteries felt normal. The pulse was usually between 90 and 100. The heart appeared to be slightly enlarged to the left, but the apex-beat could not be located. The heart-sounds were normal. The papilloedema had increased somewhat, and haemorrhages and exudates appeared in increasing numbers in both fundi. The systolic blood-pressure was 208 and the diastolic 150 mm. of Hg. There were no abnormal physical signs in the central nervous system, lungs, or abdomen. The urine contained up to 3/4th of its volume of albumin and a few granular and hyaline casts. The renal efficiency continued to fall. The standard urea clearance fell from 46 per cent. on admission to 8 per cent. shortly before death. There was no glycosuria, and repeated sugar tolerance tests were normal. The blood-count was normal and the haemoglobin 90 per cent. The platelets and bleeding time were normal. The patient began to have attacks of nocturnal dyspnoea which necessitated venesection of between 300 and 600 c.c. of blood on four occasions. Pulsus alternans was frequently present and the pulse-rate increased to between 110 and 130. The systolic blood-pressure increased to 236 and the diastolic to 170 mm. of Hg. She developed considerable oedema of the legs which was treated with repeated injections of salyrgan. She had frequent haemoptyses of frothy bright red sputum and there were numerous moist râles throughout the lungs. She developed numerous broad purple striae on the breasts and buttocks. An X-ray of the chest showed fractured 6th, 7th, and 8th left, and 9th and 10th right ribs with extensive callus formation and generalized osteoporosis. Her condition continued to deteriorate and she died quietly on January 18, 1937. At autopsy the

right adrenal gland was atrophied owing to an old thrombosis of the capsular vein. There was compensatory hypertrophy of the gland on the left side, but the weight of the two together was within normal limits. There was an adenoma of basophil cells, 0.6 cm. in diameter, in the anterior lobe of the pituitary gland. On histological examination many of the basophil cells in the rest of the anterior lobe showed the characteristic hyaline change (Crooke, 1935). There was marked cardiovascular hypertrophy, and the kidney showed the histological changes of malignant hypertension, with acute arteriolar changes in other organs.

Laboratory Investigations

(a) *Methods. Extraction of urine.* Particular attention was paid to the preservation of the urine, but the circumstances of collection in the ward, storage, and transport to the laboratory entailed deterioration in some instances. Toluene, to the amount of 1 per cent. of the volume of urine, was used as preservative, and collections were stored in a cold room. Bacterial decomposition was thus minimized, but it is suspected that enzymic action occurred. The urine was hydrolysed by boiling with acid, and then extracted with benzene, according to the method described by Callow (1936 a). Minor modifications were, however, introduced, the chief of which was the complete removal of phenolic material from the neutral benzene extract (Callow, Callow, Emmens, and Stroud, 1939). In some instances 'free' or, rather, easily liberated, material has been extracted from the cold, acidified urine, and subsequently the 'combined' androgen has been extracted after hydrolysis by boiling.

Biological assay of androgens. We are particularly indebted to Mr. C. W. Emmens and Dr. A. S. Parkes for carrying out the assay of the androgenic activity of extracts on capons at the National Institute for Medical Research. Oily solutions of the neutral fraction of the extract were assayed, as described by Emmens (1939). All assays are expressed in terms of international units of androgenic activity and the figures were obtained from a dose/response curve with androsterone, checked by control groups of birds receiving androsterone at the same time as assays of extracts were in progress. Unless otherwise stated, all assays were done on groups of five birds and the solutions administered by injection into the breast muscle. Some preliminary tests were done on single birds, and in some cases shortage of material led to administration by inunction of the comb.

Colorimetric assay of 17-ketosteroids. Colorimetric assays of methylene-ketones in the neutral fraction of the extract from hydrolysed urine were performed by the modified method described by Callow, Callow, and Emmens (1938). We are indebted to Mrs. N. H. Callow for carrying out this part of the work. This method gives a measure of the amount of 17-keto-compounds resembling androsterone or *transdehydroandrosterone*, and the result is expressed in terms of mg. of 17-ketosteroids per day's output or per litre of

urine. Examination of a variety of urines has shown that the androgenic activity per mg. of 17-ketosteroids on capons is somewhere between that of androsterone and *transdehydroandrosterone*. The relation is $y = 4.4x - 7.7$, where y = activity in international units, and x = weight in mg. of 17-ketosteroids. A chemical assay of this type, although not highly specific, gives as true an index of the excretory transformation products of the male hormone series as comb-growth assay of the complex mixture constituting the neutral 'androgenic' fraction.

(b) *Examination of urinary androgens in individual cases. Case 1* (adrenal tumour). Colorimetric assay of the first sample of urine (February 7, 1938) gave the value 40 mg. of 17-ketosteroids per diem. During the following month the figures varied a little, from 42 mg. to 64 mg. per diem, with a general tendency to rise. Capon assay on the specimen of February 13, 1938, gave a value of 145 i. u. per diem, which is definitely higher than normal. The material extracted from one specimen of urine (February 10, 1938) without hydrolysis gave figures of 1 i. u. per diem for the androgenic activity (administration by inunction) and 2.9 mg. of 17-ketosteroids. A striking change was evident in the urine immediately after operation. Three collections made (a) March 17 to 19 and 22 to 23, 1938, (b) March 27 to 29, 1938, and (c) May 9 to 10, 1938, gave the following figures for 17-ketosteroid excretion: (a) 5.4 mg. per diem, (b) 1.9 mg. per diem, and (c) 6.5 mg. per diem. These figures are actually misleadingly high, for analysis of the colour produced by the extracts with *m*-dinitrobenzene and alkali (Callow, Callow, and Emmens, 1938) showed that in the first two extracts the absorption band in the green, characteristic of 17-keto-compounds, was barely perceptible. The third extract gave a colour nearer that of a normal urine extract. Moreover, the comb-growth activity was low in all cases. Assay by inunction gave the following figures: (a) 3 i. u. per diem, (b) 2 i. u. per diem, and (c) 8 i. u. per diem. Six months after operation (September 5 to 8, 1938) the figures for androgen and 17-ketosteroid excretion were within normal limits—36 i. u. and 8.3 mg. per diem, respectively.

Summary: The urinary excretion of 17-ketosteroids in this case was about two or three times that of normal adult men. Immediately after removal of the tumour it was subnormal; two months later it was still very low, but after six months it returned to normal.

Case 2 (adrenal tumour). Urine samples from this patient were collected over a period of six months, up to her death. Neither the comb-growth assays nor the colorimetric assays form a complete uninterrupted series, but there is evidence of a fairly marked progression over the period of examination. The first urine specimen (October 19, 1936; three days; 2.62 l.) showed, by capon assay, a total excretion of 243 i. u. of androgenic activity per diem, of which 23 i. u. were extractable from the unheated urine. Thereafter the amount increased rapidly for some time. The specimen of January 15 to 21, 1937 had an androgen content of approximately 3,000 i. u. per litre, or 2,200 i. u. per diem. An assay on the

specimen of February 25 to March 4, 1937, gave a lower value of 1,360 i. u. per litre, or 730 i. u. per diem; the maximum figure was obtained with the specimen of March 25 to April 1, 1937, which gave a value of 4,000 i. u. per litre, or 1,320 i. u. per diem. Colorimetric assays began with the specimen of November 13 to 17, 1936, which gave a value of 270 mg. of 17-ketosteroids per litre, or 170 mg. per diem. A sample from the pooled extracts from the collections from November 25, 1936, to February 18, 1937, gave a value of 330 mg. per litre, or 170 mg. per diem. Figures for successive weeks' collections from the week ending February 18, 1937, until April 14, 1937, were as follows: 410 mg., 330 mg., 640 mg., 500 mg., 530 mg., 810 mg., 850 mg., 840 mg., and 770 mg. per litre, corresponding to 245 mg., 126 mg., 190 mg., 190 mg., 288 mg., 281 mg., 242 mg., and 154 mg. per diem.

Summary: The excretion of 17-ketosteroids in the urine of this case was always exceedingly high during the period of observation, beginning at a value of about 20 times the normal for an adult woman, rising to a maximum of about 35 times normal after four months, and then falling before death to the level first observed.

Case 3 (absence of adrenal tumour). The first urine specimen from this case was a three-day collection (July 29, 1937; 1.64 l.) which was extracted in two stages, after acidification in the cold, and after hydrolysis by boiling. The 'free' androgen was just detectable (about 2 i. u. per diem) whilst the excretion of 'combined' androgen amounted to about 12 i. u. per diem (test done on two birds). The second urine specimen, collected ten months later (May 29, 1938; 1 day; 0.7 l.), gave a figure of 17.8 mg. per diem for the 17-ketosteroid excretion (colorimetric assay). Examination of three specimens three months later (August 26, 1938; August 29 to September 1, 1938; September 5 to 8, 1938) gave the values 12.8, 18.6, and 14.7 mg. per diem. Four months after this (January 12, 1939) a value of 11 mg. per diem was obtained.

Summary: At first the level of androgen excretion was normal. Ten months later, the values for 17-ketosteroid excretion reached twice those for a normal adult, but the latest figure is within normal limits for an adult.

Case 4 (absence of adrenal tumour). A three-day collection of urine (October 29 to November 1, 1936; 3.28 l.) was extracted in two stages. The neutral fraction of 'free' hormone was inactive in a bantam capon in a dose equivalent to 500 c.c. injected over five days. The material liberated by hydrolysis of the urine at the boiling-point gave comb-growth (inunction method) equivalent to an androgen content of six international units per litre. The colorimetric method had not been adopted at the time these extracts were made and transferred to solution in oil.

Summary: The androgen excretion was below normal.

(c) *Chemical investigations.* Isolation of transdehydroandrosterone. The chemical examination of the urine extracts from two of these cases is not complete, but will be the subject of a further communication. A preliminary note on Case 2 has been published (Callow, 1936 b), in which the isolation of

transdehydroandrosterone was reported. This compound has also been isolated from the urine of Case 1. The procedure used is illustrated by the following example. The neutral fraction of the benzene extract from 5.25 l. of urine (Case 2, November 1936), weighing 1.75 gm., was heated with 10 gm. of Girard's reagent T in 25 c.c. of glacial acetic acid for half an hour on the water bath. The product was poured into water and the non-ketonic fraction extracted with ether. The residue was then decomposed by warming, after addition of dilute sulphuric acid, and the ketonic fraction extracted with ether. The non-ketonic and the ketonic fractions weighed, respectively, 0.41 and 0.97 gm. An approximate capon assay showed that androgenic activity was concentrated in the ketonic fraction. One bird, receiving non-ketonic fraction equivalent to 125 c.c. of urine over five days, showed a comb-growth (L + H) of 3.5 mm., whilst a second, receiving the same equivalent of the ketonic fraction, showed a comb-growth of 14.5 mm. The ketonic fraction was dissolved in a little dry pyridine and the solution treated with benzoyl chloride in slight excess. Water was then added cautiously, and the precipitated oil was washed free from pyridine, and warmed with methanol. A crystalline material separated, weight 390 mg., m. p. 220–240° C. Recrystallized from ethyl acetate, *transdehydroandrosterone benzoate* was obtained with m. p. 245–254° C. A mixture with an authentic specimen (m. p. 254–257°) melted at 251–257° C. By hydrolysis, *transdehydroandrosterone*, m. p. 136–139° C, $[\alpha]_D^{25} + 13^\circ$ in ethyl alcohol, was obtained and converted into the acetate, m. p. 162–166° C.; the identity of these compounds was confirmed by mixed m. p. with authentic specimens.

This process was repeated subsequently with extracts from the same urine (Case 2), and it was also found that, in material so rich in *transdehydroandrosterone*, the first stage of separation of the ketonic fraction was unnecessary. Approximately, the weight of *transdehydroandrosterone benzoate* separated as the crude benzoate accounted for 70 per cent. of the comb-growth activity of the extracts. Extracts from the urine of Case 1 yielded *transdehydroandrosterone benzoate* by direct benzylation, in a yield of 7 mg. of crude product per litre, but fractional crystallization was necessary to separate it from other crystalline material, the nature of which is now under investigation.

(d) *Androgen assays on serum and tumour tissue.* The methods of extraction of androgens from serum and tissue are not as well understood as those of extraction from urine. We have, however, carried out extractions from the sera and tumour tissues of Cases 1 and 2, and on sera from a group of normal males, for the collection of which we are indebted to Mrs. M. Boycott, University College Hospital. The method of extraction employed was derived from that of Freed (1936). After precipitation of the serum with acetone, the supernatant liquid was evaporated and the watery residue made up to five times the original volume of the serum with water, 2 per cent. by volume of concentrated hydrochloric acid added, and the mixture boiled for one hour under reflux. The product was extracted with ether,

and the extract washed, dried over sodium sulphate, and evaporated. The residue was taken up in oil for administration to capons by inunction. An extract from the mixed sera of five normal men gave a response equivalent to six international units of androgenic activity per litre of serum. Serum from Case 1 (February 18, 1938) contained 15 i. u. per litre. Serum from Case 2 (March 10, 1937) contained 6 i. u. per litre.

The tumour tissue from Case 2 was partly necrotic. At *post mortem* it was divided as far as possible into necrotic and undeteriorated tissue, and these were sliced finely and extracted with successive lots of acetone. The acetone extracts were evaporated to dryness and extracted with methanol. Evaporation of the methanol left residues (a) weighing 56 gm. with an androgenic activity of 1 i. u. per gm. from the necrotic tissue, and (b) weighing 35 gm., with an activity of 0.35 i. u. per gm. from the living tumour tissue. Thus only about 70 i. u. were extracted from the whole tumour, the weight of which was about 5 kg. The liver, which contained some metastatic tumour tissue, yielded 49 gm. of extract with an activity of 0.5 i. u. per gm.

The tumour from Case 1 yielded, by a similar extraction, 14 gm. of extract with an activity of 0.2 i. u. per gm.

With the reservation due to our ignorance of the optimal methods of extraction, these results suggest that androgenic material is not stored in the tumour tissue, nor does it remain long in the circulation, but is excreted rapidly in the urine.

(e) *Other hormone estimations.* Certain other estimations were carried out on the urine and serum of these patients. The estimations of urinary oestrogen are of interest in view of the reports that large amounts occur in the urine of adrenal cortical tumour cases (Frank, 1934, 1937; Graef, Bunim, and Rottino, 1936; Saphir and Parker, 1936; Burrows, Cook, Roe, and Warren, 1937). We have not found values grossly above normal, and in this respect agree with Simpson, de Fremery, and Macbeth (1936), Slot (1936), and Kenyon, Gallagher, Peterson, Dorfman, and Koch (1937).

Case 1. Oestrogen estimations on specimens of urine before operation, collected February 3, 1938 (morning specimen), and February 23 to 24, 1938, gave figures of less than the equivalent of 7 μ g. oestrone per litre and about 10 μ g. per day respectively. The second figure is high in comparison with results on bulk collections from normal men (Callow, Callow, Emmens, and Stroud, 1939), but not grossly abnormal.

Case 2. In the urine collection of October 19, 1936, the 'free' oestrogen was equivalent to 1 μ g. oestrone per litre, and the 'combined' oestrogen equivalent to 4 μ g. per litre. The excretion was, therefore, not grossly excessive.

Case 4. Tests for 'free' and 'combined' oestrogen in the urine indicated the presence of amounts rather below normal. Negative results were obtained in tests for thyrotropic, gonadotropic, antigonadotropic, and lactogenic hormones in the serum. We are indebted for the tests on the urine of this patient to Miss M. H. MacKenzie, of the Pregnancy Diagnosis Station,

Edinburgh, and to Dr. A. S. Parkes and Dr. I. W. Rowlands of the National Institute for Medical Research.

Discussion

The association of adrenal cortical tumour with basophilism is curious; it is obviously not a direct, but an indirect or secondary phenomenon, as each condition can occur without the other. When the two are associated, age and sex are obviously important, adrenal cortical tumour being rare in basophilism in the adult male, the rule in basophilism in the child, and common in basophilism in the adult female. Thus in the literature we have found only one example of the association in the adult male, while another is reported in this paper, and no example of basophilism in a child in whom adrenal tumour was absent, though an exception is reported in this paper. It is to be remembered that in all cases of basophilism, whether an adrenal cortical tumour is present or not, hyaline change in the basophil cells of the pituitary is always present (Crooke, 1938). Kepler, Walters, and Piper (1938) have suggested that these two forms can be separated on clinical evidence alone. They stated that in females with an adrenal cortical tumour there is enlargement of the clitoris and other evidences of 'masculinization', and that the obesity does not have the characteristic 'buffalo type' with a cervical hump of fat. In certain cases of adrenal tumour a palpable tumour makes the diagnosis obvious. In some, enlargement of the clitoris and other evidence of masculinization as described by Kepler, Walters, and Piper are present, but cases also occur in which these clinical features are lacking, and we cannot accept the distribution of obesity in these cases as distinctive. In the absence of distinctive clinical features two further methods of investigation are available: (1) X-ray examination after perirenal insufflation with air, and (2) determination of urinary androgen excretion.

The technique of X-ray after perirenal insufflation with air as described by Cahill (1935) is simple, and in our limited experience has given rise to no difficulties. In Case 1 excellent delineation of the tumour was obtained by this means. In Case 2 the tumour was palpable and X-ray examination was not required.

The excretion of androgens in the urine of these four examples of basophilism shows a striking difference between the two cases in which an adrenal cortical tumour was present and the other two in which such a tumour was absent. In Case 1 the values (from 40 up to 64 mg. per diem) fall well outside the normal range, while in Case 2 the divergence is extreme, the values ranging from 120 to 288 mg. per diem. This increase appears to be due largely to *transdehydroandrosterone*, which was isolated from both cases in large amounts—7 mg. per litre in Case 1 and 70 mg. per litre in Case 2—as compared with a normal excretion of 0.1 to 0.2 mg. per litre (N. H. Callow, 1939, and unpublished work). In another tumour case (under the

observation of Dr. S. Levy Simpson, unpublished) this compound has also been isolated in correspondingly large amounts.

On the other hand, the androgen excretion in the two cases of advanced basophilism without adrenal cortical tumour shows a figure a little above the normal in Case 3 (11 to 18 mg. per diem) and a low value on biological assay, and 6 i. u. of androgenic activity, in Case 4. Unfortunately, in this case a colorimetric assay was not made, but the biological assay leaves little doubt that this would have been low. It is therefore clear that the clinical symptoms of basophilism may be severe without a great rise in the urinary excretion of androgens or 17-ketosteroids if no tumour of the adrenal cortex is present.

Excretion of large amounts of androgenic substance in the urine in a patient with basophilism and adrenal cortical tumour has also been reported by Simpson, de Fremery, and Macbeth (1936), who found between 200 and 400 i. u. per litre in the urine of their female patient. A similar excretion of androgenic substances in the urine has been found in patients with adrenal cortical tumour without basophilism. Cahill, Loeb, Kurzrok, Stout, and Smith (1936) described two cases of 'virilism' associated with adrenal cortical carcinomata. In one, 480 i. u. of male hormone activity was excreted per diem, whilst in the other the amount was 69 i. u., a figure which Gallagher, who carried out the assays, regarded as outside the limits of normal variation on the basis of the methods and normal samples then available (Kenyon, Gallagher, Peterson, Dorfman, and Koch, 1937). Slot (1936) described a case of 'hypernephroma' in which the excretion of male hormone was 2,200 i. u. per litre.

It would seem, therefore, that an increased level of androgenic activity in the urine is a characteristic feature of patients with adrenal cortical tumours. Caution is, however, necessary in interpreting the significance of increased androgen excretion, since some cases of 'virilism' in which no adrenal tumour was found have been shown to excrete amounts of androgenic substance excessive in comparison with the normal, though commonly much smaller than in the cases with adrenal cortical tumours (Gallagher, Peterson, Dorfman, Kenyon, and Koch, 1937; Glass and Bergman, 1938; Broster, Allen, Vines, Patterson, Greenwood, Marrian, and Butler, 1938; Dingemans and Laqueur, 1938).

We have studied a series of 10 cases of hirsutism in women without clinical evidence of adrenal tumour, and these have been supplemented by a number of cases from which urine samples have been sent to one of us for hormone assay by the kindness of various clinicians who have been interested in this work. Of a total of 26 cases, 14 come within our conception of the limits of normal variation, based on 11 patients, whilst 12 others form a series, without an obvious gap, with increasing values up to nearly three times the highest found in a normal woman.

The diagram (Fig. 1) illustrates the varying ranges of values for androgen excretion as determined colorimetrically for normal and pathological cases.

In the three groups of normal men, normal women, and cases of 'virilism', each dot represents a value for a single patient (generally a mean value for several samples) falling within a certain range. Most of the normal men exhibit values of between 5.1 and 10 mg. per diem, the mean value being 9.9 mg. per diem. The normal women show a mean value of 6.4 mg. per diem, and individuals generally come within the ranges of 0 to 5 and 5.1 to

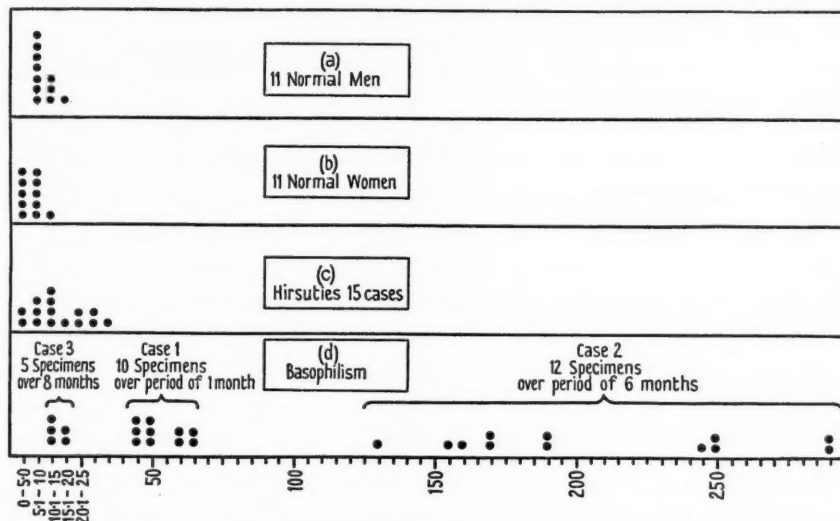


FIG. 1. Diagrammatic comparison of ranges of 17-ketosteroid excretion in mg. per diem of (a) normal men, (b) normal women, (c) cases of 'virilism' without adrenal cortical tumour, and (d) Cases 1, 2, and 3 of basophilism.

10 mg. per diem. In cases of 'virilism' without adrenal tumour (as far as can be demonstrated) all ranges from 0 to 5 to 30.1 to 35 mg. per diem are represented, and it is, therefore, impossible to consider any value up to 35 mg. per diem. as, by itself, diagnostic of an adrenal tumour. At the bottom section of the diagram are represented the values for 17-ketosteroid excretion found on various examinations of urine from the first three cases described in this paper. The fourth case in which biological assay gave a very low figure is not included here, because no colorimetric assay was made.

A very high level of excretion of 17-ketosteroids or androgenic substances in cases of basophilism has been found only in those with an adrenal cortical tumour. The relatively simple colorimetric method of estimating 17-ketosteroids in urine should prove a useful adjunct in the diagnosis of future cases.

Summary

1. Four cases of basophilism, or Cushing's syndrome, are described. In two of these a malignant adrenal cortical tumour was present; in one of

these the tumour was palpable, in the other it was demonstrated by X-ray after perirenal insufflation of air. The diagnoses were subsequently confirmed, in one at post-mortem examination, in the other at operation.

2. The urine of these two patients gave high values in the colorimetric assay of 17-ketosteroids or in the biological assay of androgens. This increase of 17-ketosteroids was largely due to *transdehydroandrosterone* which was isolated from the urine in amounts many times as great as those occurring in normal men and women. The other two cases, in which no adrenal tumour was present, gave low values by comparison in the colorimetric or biological assay.

3. It is claimed that determination of 17-ketosteroids in urine gives valuable assistance in determining the presence of adrenal cortical tumours in cases of basophilism.

We are indebted to Professor Arthur Ellis for his assistance and for permission to publish two of the cases, and to Dr. Maitland Jones and Dr. Tallerman for permission to publish the other cases.

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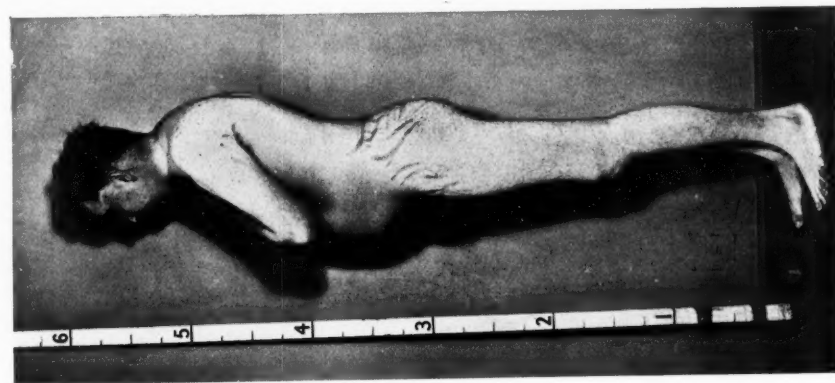


FIG. 2. Case 1. Before operation, 4.2.38

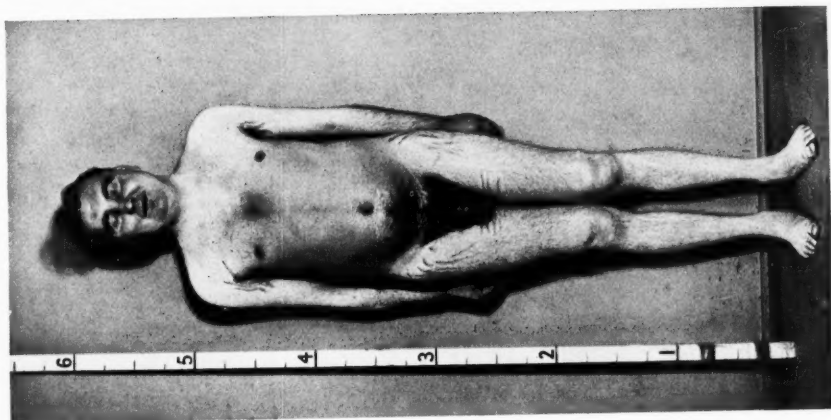


FIG. 3. Case 1. Before operation, 4.2.38

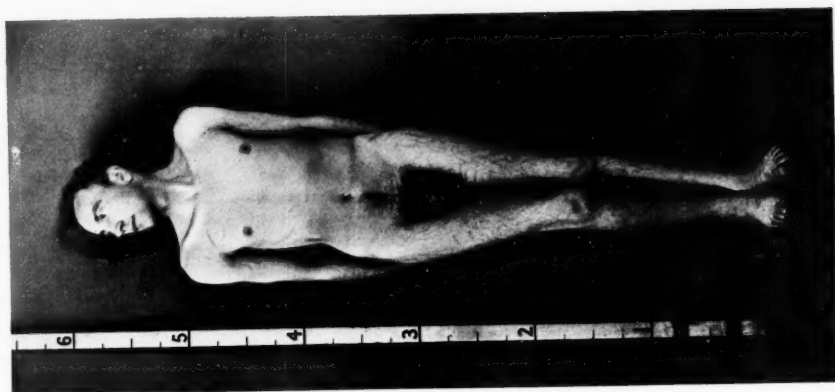
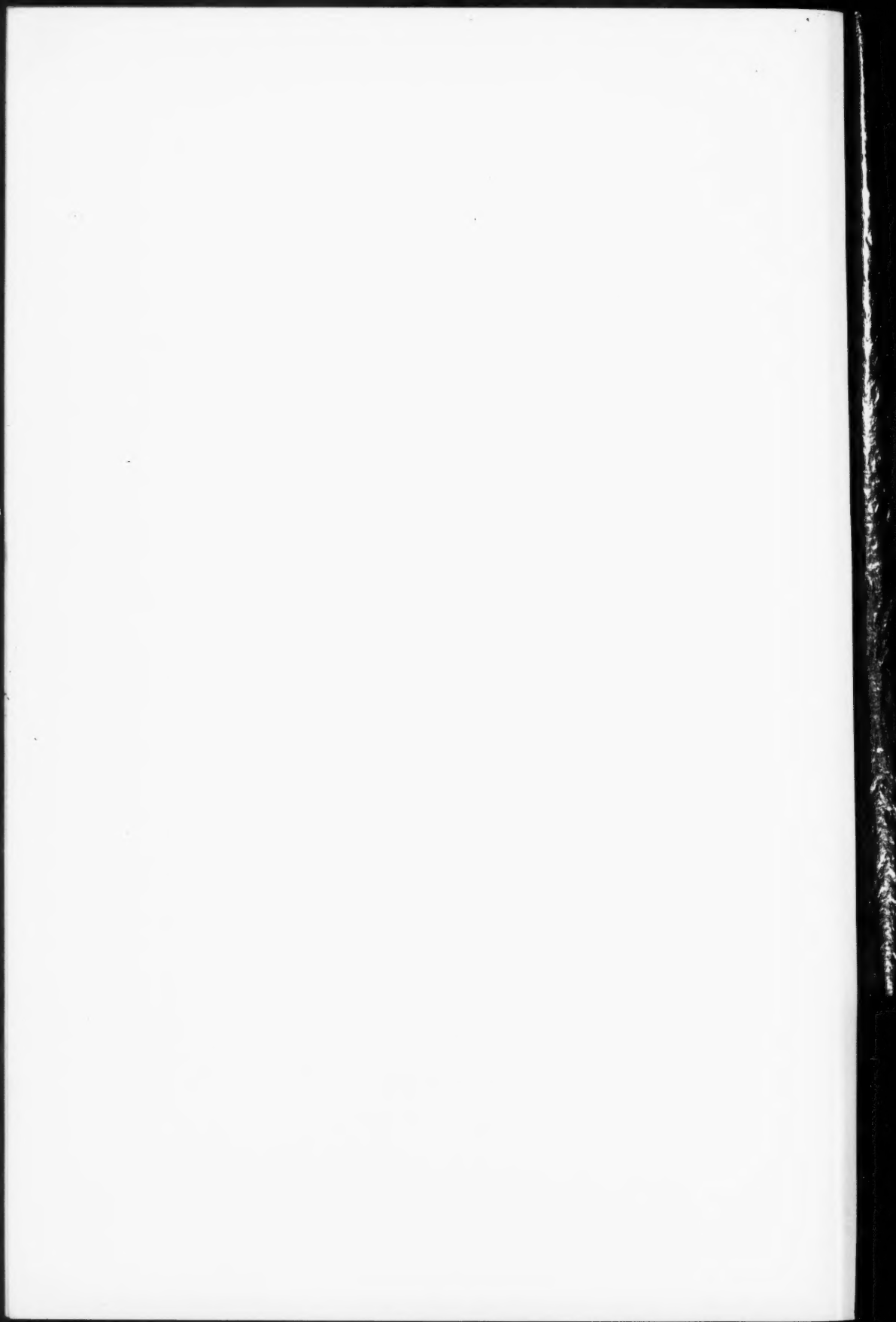


FIG. 4. Case 1. Six months after operation



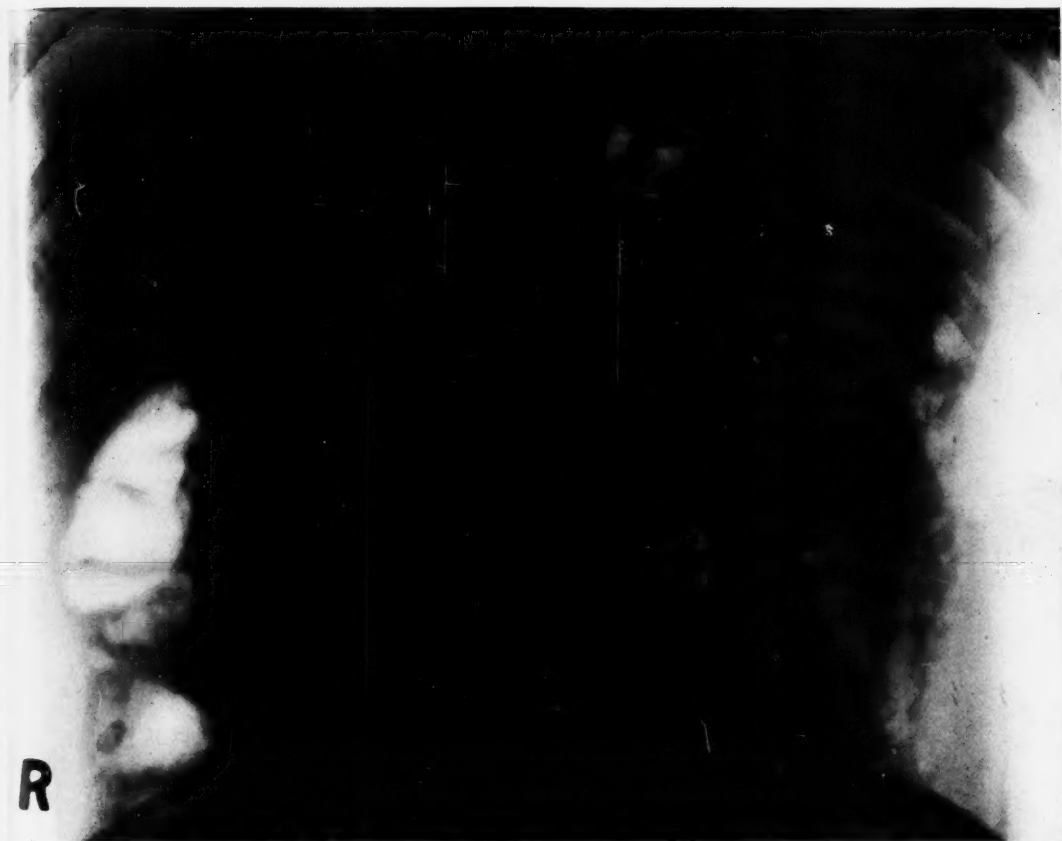


FIG. 5. Case 1. X-Ray taken after perirenal insufflation showing left adrenal tumour outlined by air

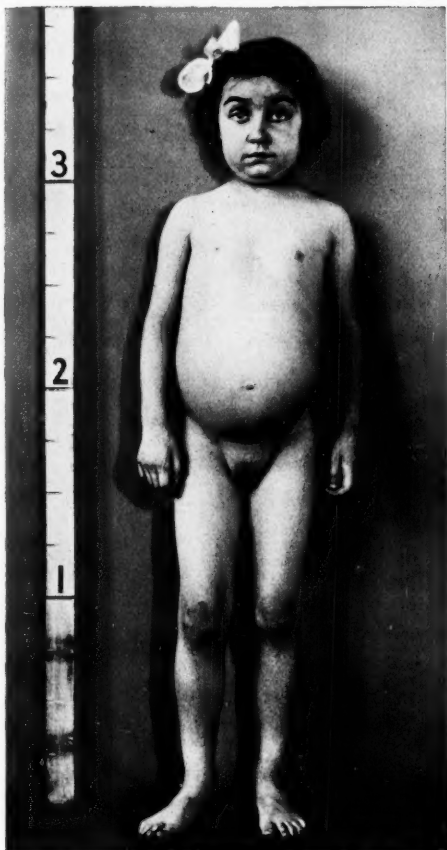


FIG. 6. Case 2. On first admission, 7.8.36



FIG. 7. Case 2. Two weeks before death

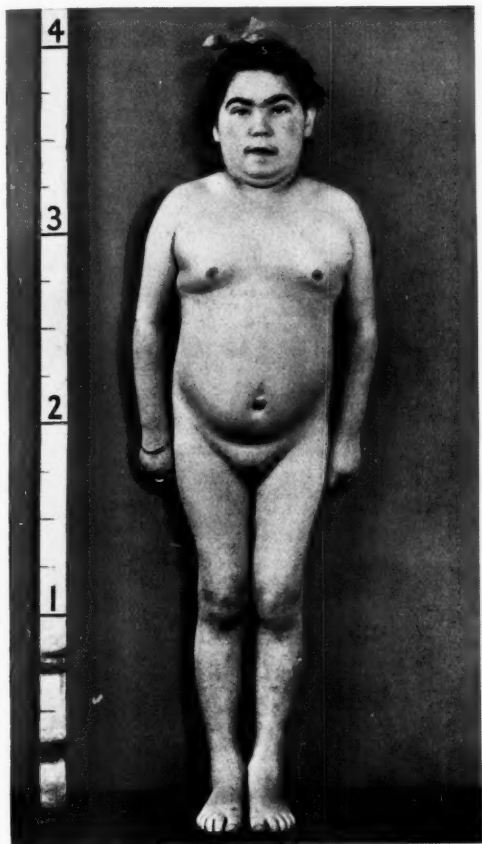


FIG. 8. Case 3. Before operation

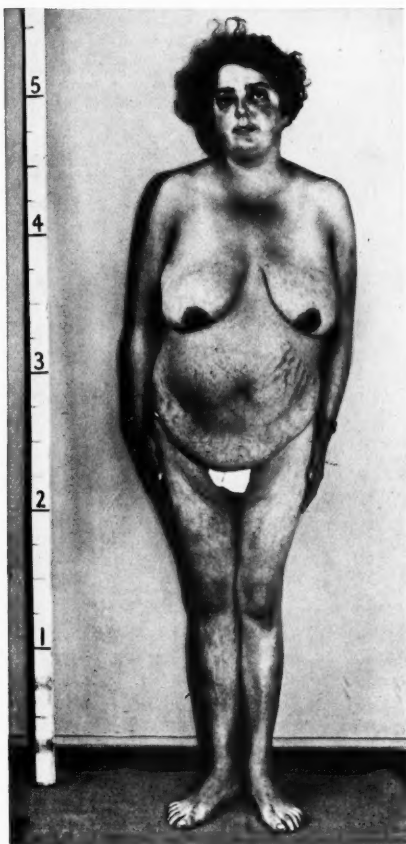
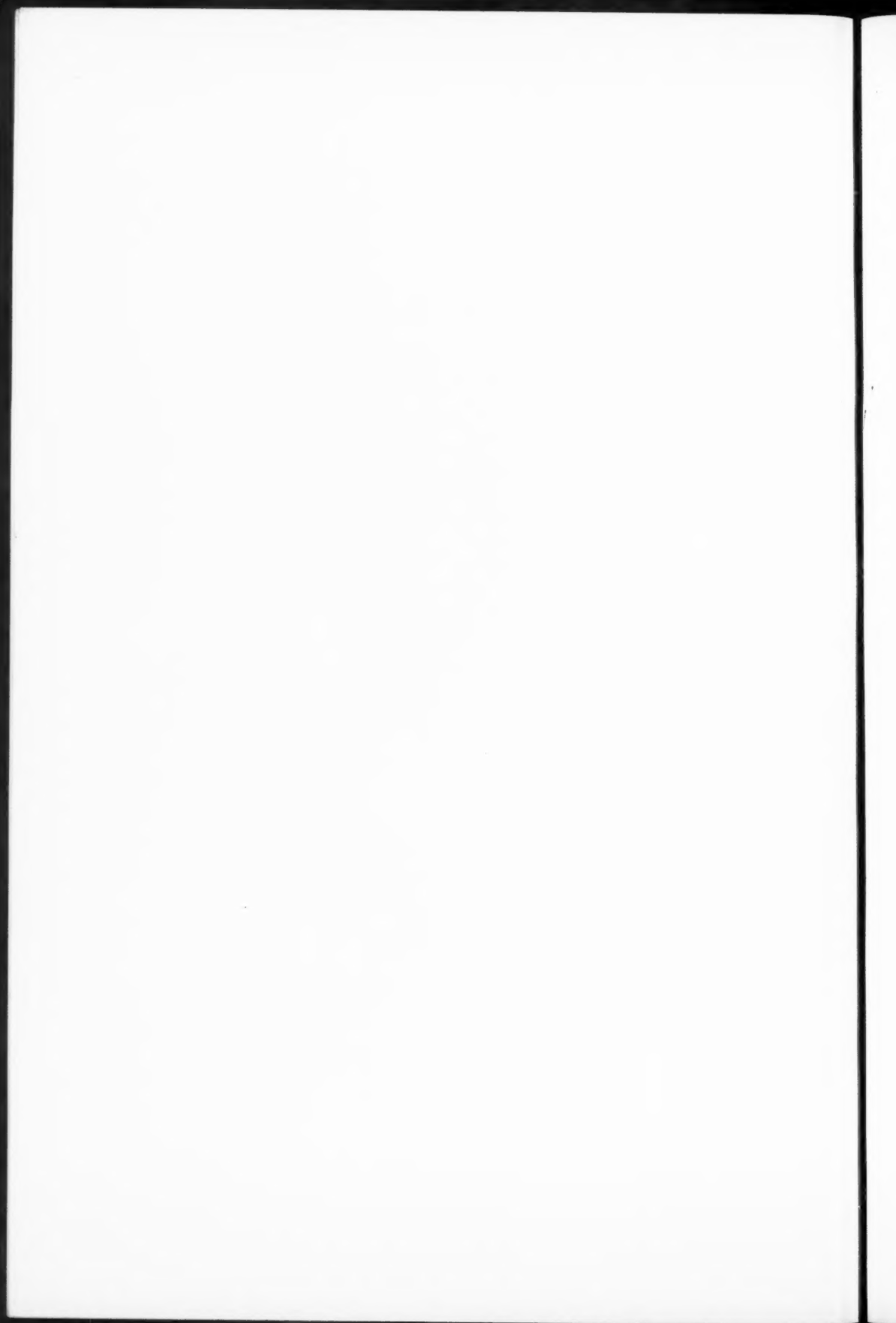


FIG. 9. Case 4. Three months before death



THE CAUSATION OF THE LOW BLOOD-SUGAR CURVE IN COELIAC DISEASE¹

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Introduction

CONVINCING evidence has been brought forward by Thaysen (1929 *b*, 1932, 1935) that tropical and non-tropical sprue in adults and coeliac disease in children are essentially identical conditions, and he has grouped the three together as subdivisions of 'idiopathic steatorrhoea', a syndrome which has also been referred to as 'Gee-Thaysen disease'. In 1926 Thaysen first drew attention to the abnormally small rise in the blood-sugar content following the ingestion of glucose in cases of non-tropical sprue. In subsequent papers (Thaysen, 1929 *a*, 1932, 1935; Thaysen and Norgaard, 1929) he extended this observation and defined the low blood-sugar curve as one showing a rise of 40 mg. per 100 c.c. or less during two hours following the ingestion of 60 gm. of glucose in adults. He showed such a curve to occur as an inconstant phenomenon in 5 per cent. of normal subjects, while in non-tropical sprue it occurred fairly constantly in 50 per cent. of the cases. Thaysen's findings in non-tropical sprue have been confirmed by many later observers (Holst, 1927; Engel, 1931; Bennett, Hunter, and Vaughan, 1932; Thorfinn, 1933; Anderson and Lyall, 1933; Moore, O'Farrell, Geraghty, Hayden, and Moriarty, 1936; Mogensen, 1937; Nussbrecher and Morton, 1937). A similar low blood-sugar curve in children suffering from coeliac disease was demonstrated independently by Fanconi (1928), Svensgaard (1929), and MacLean and Sullivan (1929), and their findings have been frequently confirmed (Thaysen, 1929 *b*; MacRae and Morris, 1931; Badenoch and Morris, 1936). The low curve appears to be a more constant feature of coeliac disease than of sprue.

The present paper is concerned with the cause of the low blood-sugar curve in coeliac disease. Accepting Thaysen's contention that sprue and coeliac disease are essentially the same condition, deductions from biochemical changes found in one should be applicable to the other.

The origin of the low blood-sugar curve in these conditions has been the subject of considerable experiment and discussion. The possible causes of such a curve are:

1. Lowered renal threshold to glucose.

¹ Received April 25, 1939.

2. Diminished or delayed absorption of sugar from the bowel.
3. Increased rate of utilization or storage of glucose in the tissues following absorption.

MacLean and Sullivan (1929) investigated the possibility of a lowered renal threshold to glucose and showed that glycosuria was not a feature of the patients showing the low blood-sugar curve; its occurrence in one of their 14 cases must be regarded as a coincidence. Their observations have been abundantly verified by subsequent observers (Svensgaard, 1931; MacRae and Morris, 1931; Badenoch and Morris, 1936). The low curve must, therefore, be caused either by faulty absorption or by an abnormality of the intermediary carbohydrate metabolism. In view of the generally accepted fact that there is defective fat absorption in idiopathic steatorrhoea, a similar abnormality of carbohydrate absorption seems the likely explanation of the low blood-sugar curve, and this view has been supported by the observations of MacRae and Morris (1931), Badenoch and Morris (1936), Fairley (1936), Ross (1936), and Nussbrecher and Morton (1937). The opposing view, however, that an abnormality of the intermediary carbohydrate metabolism is present, was put forward by Thaysen (1929 *a*, 1932, 1935) and has received support from Mogensen (1937).

As abnormalities in the blood-sugar curve after oral administration of glucose may be caused either by defective absorption from the bowel or by disturbance of intermediary metabolism, the most direct evidence of the latter should be afforded by a study of the response to intravenously injected glucose; for, by this procedure, variations caused by alterations in the rate of absorption of glucose from the bowel are excluded. Rapid removal of injected glucose from the blood indicates increased rate of storage, utilization, or excretion; conversely, slow disappearance of the excess sugar from the blood gives evidence of defective storage power, or of a diminished rate of utilization or excretion. Thaysen (1929 *a*) and Mogensen (1937) found a rapidly falling blood-sugar curve following intravenous injection of glucose, indicating increased glucose tolerance, whereas Fairley (1936) and Ross (1936) found high, slowly falling curves indicative of impaired glucose tolerance. Previous work on this question having yielded such discordant results, the present investigation was undertaken in an attempt to arrive at some definite decision.

The Intravenous Curve in Normal Subjects

Owing to the wide variations in the response to the intravenous injection of glucose found in normal subjects by different workers, variations probably due to difference in technique, the investigations on coeliac disease were preceded by a detailed examination of the response of healthy children and adults to the intravenous injection of glucose. This work has already been published (Crawford, 1938) and the relevant features are briefly summarized here:

A test dose of 0.5 gm. of glucose per kg. body-weight, as a 20 per cent. solution in normal saline, is injected intravenously following an eight-hour fast. Capillary blood is removed for sugar estimation prior to the injection, two minutes after its completion, and at fifteen-minute intervals until ninety minutes after the injection. Tolerance is gauged by noting the time after the injection at which the blood contains a sugar concentration of 100 mg.

TABLE I

Intravenous Glucose Tolerance Tests in Normal Subjects.

| Age group. | Time of fall of blood-sugar to 100 mg. per 100 c.c. |
|--------------|--|
| 0 to 2 years | 30 to 45 minutes |
| 2 to 4 " | 45 to 60 " |
| 4 to 10 " | 45 to 75 " |
| Over 10 " | 60 to 75 " |

per 100 c.c. or less—the upper limit of normal fasting blood-sugar values with the technique employed. The time at which this occurs was shown to be constant for the individual under standard conditions and to vary within definite limits among normal subjects. It was shown that, with normal intermediary mechanism the blood-sugar reached a level of 100 mg. per 100 c.c. at thirty, forty-five, sixty, or seventy-five minutes after the injection according to the age of the subject (Table I). The amount of sugar excreted in the urine after the injection varied from 3 to 9 per cent. of the injected glucose.

Ross (1938) has recently criticized the value of this series of normal curves on the grounds that the subjects were 'convalescents'. The great majority, however, were many weeks recovered from ailments unassociated with disturbance of carbohydrate metabolism; the remainder were healthy, active subjects. As the curves from the 'healthy' and the 'convalescent' subjects were similar in all respects, it seems probable that the series as a whole may be regarded as normal.

The Intravenous Curve in Coeliac Disease

Twelve well-established cases of coeliac disease have been investigated. All but one (Case 10) showed a rise of less than 40 mg. per 100 c.c. in the blood-sugar level following the ingestion of 2 gm. glucose per kg. of body-weight. The remaining case showed the alternative 'low-level' curve described by Thaysen (1929*a*, 1932), the blood-sugar rising from the low fasting level of 56 mg. per 100 c.c. to a maximum height of 106 mg. per 100 c.c. at one hour. The results of the oral glucose tolerance tests are given in Table II. Using the technique described above, intravenous glucose tolerance tests were carried out during an active period of the disease in all 12 cases; in five cases the test was repeated during a quiescent phase. The results of these tests are detailed in Table III. In every instance, during both active and quiescent phases, the time of fall of the blood-sugar to normal fasting levels was within the normal limits defined in Table I.

Sugar excretion in the urine was also within normal limits in each of the seven cases in which it was estimated. In Table IV the cases are subdivided into age groups and compared with the average findings from normal subjects

TABLE II

Blood-sugar Curves after Oral Glucose (2 gm. per kg. of body-weight) in 12 Cases of Coeliac Disease.

| Case. | Blood-sugar in mg. per 100 c.c. | | | | | | | | | Maximum rise of blood-sugar mg. per 100 c.c. |
|-------|---------------------------------|---------|---------|---------|---------|---------|---------|----------|----------|--|
| | Fast-ing. | 15 min. | 30 min. | 45 min. | 60 min. | 75 min. | 90 min. | 105 min. | 120 min. | |
| 1 | 79 | 110 | 100 | 111 | 110 | 97 | 110 | — | 107 | 32 |
| 2 | 57 | — | 93 | — | 70 | — | 79 | — | 77 | 36 |
| 3 | 70 | 68 | 75 | 78 | 90 | 91 | 86 | 93 | 101 | 31 |
| 4 | 88 | 108 | 106 | 111 | 113 | — | 115 | — | 111 | 27 |
| 5 | 70 | 68 | 75 | 72 | 77 | — | 74 | — | 77 | 7 |
| 6 | 44 | — | 47 | — | 59 | — | 77 | — | 74 | 33 |
| 7 | 66 | — | 81 | — | 88 | — | 84 | — | 79 | 22 |
| 8 | 65 | — | 60 | — | 83 | — | 74 | — | 68 | 18 |
| 9 | 77 | — | 95 | — | 101 | — | 104 | — | 88 | 27 |
| 10 | 56 | — | 59 | — | 106 | — | 92 | — | 95 | 50 |
| 11 | 70 | — | 81 | — | 88 | — | 86 | — | 88 | 18 |
| 12 | 79 | — | 112 | — | 90 | — | 95 | — | 75 | 33 |

TABLE III

Intravenous Glucose Tolerance Tests in 12 Cases of Coeliac Disease.

| Case. | Age in years. | Weight in kg. | Blood-sugar in mg. per 100 c.c. | | | | | | | | | Sugar in urine following injection; per cent. of injected glucose. | Clinical condition. |
|-------|------------------|---------------|---------------------------------|--------|---------|---------|---------|---------|---------|---------|--------|--|---------------------|
| | | | Fasting. | 2 min. | 15 min. | 30 min. | 45 min. | 60 min. | 75 min. | 90 min. | | | |
| 1 | 2 3/12 | 10.0 | 88 | 284 | 181 | 115 | 74 | 68 | 57 | 51 | — | Quiescent | |
| 2 | 1 2/12 1 6/12 | 5.25 | 74 | 308 | 213 | 125 | 75 | 68 | 64 | 77 | — | Active | |
| | | 61 | 260 | 146 | 97 | 57 | 56 | 63 | 70 | — | Active | | |
| | | 5.4 | 84 | 314 | 168 | 134 | 95 | 75 | — | — | — | Quiescent | |
| 3 | 3 | 11.7 | 52 | 202 | 132 | 113 | 95 | 73 | — | — | 3.3 | Active | |
| | | | 66 | 270 | 177 | 129 | 93 | 79 | 79 | 72 | 5.3 | Active | |
| | | | 77 | 296 | 181 | 121 | 96 | 86 | 75 | — | 6.1 | Quiescent | |
| 4 | 9 | 15.2 | 77 | 278 | 177 | 117 | 84 | 83 | 81 | 83 | 8.2 | Active | |
| | | | 93 | 282 | 211 | 110 | 77 | 77 | — | — | — | Quiescent | |
| 5 | 2 4/12 | 11.5 | 74 | 355 | 163 | 134 | 106 | 70 | — | — | — | Active | |
| | | | 81 | 340 | 157 | 130 | 104 | 79 | 76 | 80 | 5.4 | Quiescent | |
| 6 | 1 4/12 | 7.0 | 66 | 230 | 166 | 122 | 95 | 93 | 83 | 75 | — | Active | |
| 7 | 1 7/12 | 7.1 | 74 | 274 | 182 | 145 | 95 | 92 | — | — | — | Active | |
| 8 | 1 8/12 | 7.3 | 75 | 230 | 139 | 110 | 83 | 72 | — | — | — | Active | |
| 9 | 5 | 13.6 | 75 | 296 | 190 | 104 | 75 | 83 | 86 | 79 | 4.3 | Active | |
| 10 | 5 | 10.4 | 83 | 240 | 172 | 111 | 81 | 77 | 74 | 86 | 4.7 | Active | |
| 11 | 8 | 15.2 | 75 | 304 | 209 | 166 | 112 | 86 | 72 | — | 3.8 | Active | |
| 12 | 1 4/12 | 7.0 | 66 | 281 | 188 | 139 | 84 | 70 | 62 | — | — | Active | |

of the same age, the average age of coeliac patients and normal subjects in each age group being the same. It will be seen that the times at which normal fasting levels are regained are the same in patients and controls, and the slight differences found between the average curves from the coeliac

patients and the corresponding figures from normal subjects cannot be regarded as significant; the tendency to lower levels in the coeliac curves no doubt reflects the low fasting blood-sugar values found in many of these cases. Fig. 1 shows composite curves constructed from the results of tests carried out during active and quiescent phases of the disease in Cases 1 to 5. Here again there is no significant difference.

TABLE IV

Mean Figures from Intravenous Glucose Tolerance Tests in Coeliac Disease and Normal Children, Divided in Age Groups.

| Time of Specimen. | 0 to 2 years. | | 2 to 4 years. | | 4 to 9 years. | |
|-------------------|------------------------------------|-----------------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|
| | 5 Coeliacs. Mg. per 100 c.c. | 6 Normals. Mg. per 100 c.c. | 3 Coeliacs. Mg. per 100 c.c. | 10 Normals. Mg. per 100 c.c. | 4 Coeliacs. Mg. per 100 c.c. | 10 Normals. Mg. per 100 c.c. |
| Fasting | 66 | 71 | 71 | 81 | 77 | 86 |
| 2 min. | 243 | 238 | 311 | 315 | 280 | 315 |
| 15 " | 161 | 158 | 184 | 198 | 187 | 204 |
| 30 " | 125 | 116 | 129 | 138 | 125 | 143 |
| 45 " | 90 | 88 | 91 | 93 | 89 | 97 |
| 60 " | 80 | 77 | 72 | 76 | 82 | 81 |

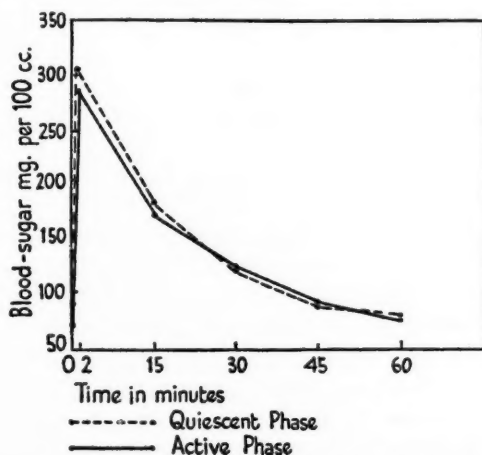


FIG. 1. Mean intravenous curves during active and quiescent phases in five cases of coeliac disease

Discussion

From these results it does not appear that there is any abnormality in the intermediary metabolism of carbohydrate in coeliac disease. In view of this, and as all the evidence points to there being no abnormality in the renal threshold, the remaining hypothesis, namely, defective absorption from the bowel, seems to be the most likely explanation of the low blood-sugar curve. Ross (1936) has reached a similar conclusion based upon very different experimental findings. Using a different technique from that employed in

the present investigation he found a high, slowly falling curve after the intravenous injection of glucose in cases of coeliac disease. He argued that this impairment of carbohydrate tolerance was the result of carbohydrate starvation, a condition shown by Himsworth (1933, 1935) to produce an impairment of tolerance as gauged by the oral test. Thus, in spite of the presence of carbohydrate in the diet, the patients showed a curve characteristic

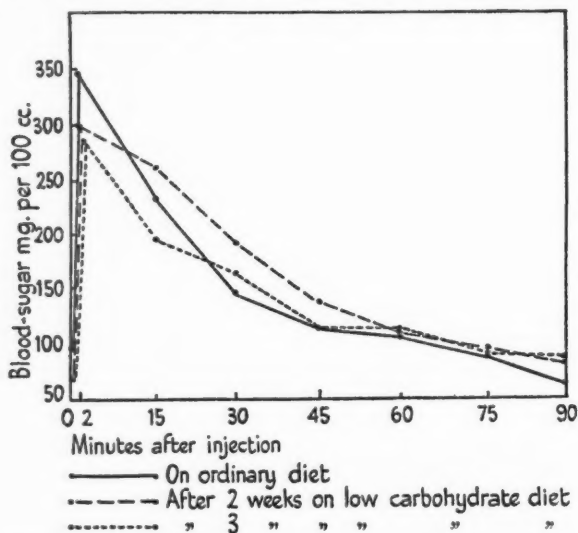


FIG. 2. Intravenous glucose tolerance tests in a healthy child aged 8 years, on ordinary diet and on a low carbohydrate diet for three weeks

of carbohydrate starvation, and from this Ross concluded that carbohydrate was not being absorbed. It seems probable, however, that carbohydrate deprivation in coeliac disease is rarely severe, for ketonuria is seldom seen; none of the cases in the present series gave a positive Rothera's test at the time when the low oral blood-sugar curve was obtained. It is known that if carbohydrate deprivation is persisted in over a prolonged period the ketonuria diminishes, but it does not disappear completely unless the deprivation is of quite a mild degree. In our experience even severe carbohydrate starvation does not interfere with the tolerance to *injected* glucose. This is illustrated by the experiment recorded in Fig. 2 which shows curves obtained from a healthy child kept for three weeks on a diet severely restricted in carbohydrate. Though gross ketonuria persisted throughout this period, no impairment of glucose tolerance, as gauged by the intravenous test, occurred. Closely comparable results have been obtained from four other subjects.

Thaysen (1929 *a*, 1932) demonstrated in patients with idiopathic steatorrhoea that the respiratory quotient, following ingestion of carbohydrate, rose to levels which indicated that considerable quantities of sugar were being metabolized, and he also showed that these patients yielded a higher respiratory quotient when given a high carbohydrate diet than when on

ordinary diet. Thaysen regarded these results as indicating that there was no interference with carbohydrate absorption, but, as MacRae and Morris (1931) have pointed out, these results merely show that there was not an absolute failure of carbohydrate absorption; they do not exclude the possibility of delayed or inefficient absorption. Indeed the striking point which Thaysen's experiments show is that there is no failure on the part of the

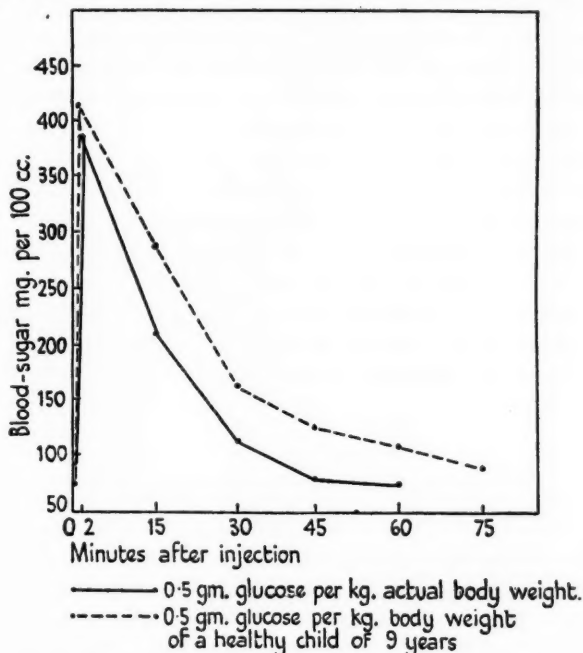


FIG. 3. Effect of increased dosage of glucose on intravenous glucose tolerance test in a case of coeliac disease, aged 9 years and weighing 15.2 kg.

tissues in coeliac disease to oxidize carbohydrate. This, taken in conjunction with the fact that ketosis is not a feature of coeliac disease, and with the experimental findings recorded in Fig. 2, suggests that it is improbable that there is sufficient deprivation of carbohydrate in coeliac disease to cause intolerance to intravenous glucose. There can be little doubt that the discrepancies between the results obtained by Ross and those arrived at in the present investigation depend on differences in the technique employed in carrying out the intravenous glucose tolerance tests. The essential difference lies in the dosage of glucose. In the present series a dose of 0.5 gm. of glucose per kg. of body-weight has been used, whereas Ross employed a standard dose of 10 gm. of glucose both for normal and coeliac cases, irrespective of body-weight. He does not report the weights of his coeliac patients, but as these children are usually from 30 to 50 per cent. below the weight of healthy children of the same age, it is evident that his patients received, relative to body-weight, a much larger dose of glucose

than did his normal subjects. The results of the administration of such increased dosage of glucose to a child with coeliac disease are shown in Fig. 3. In this case, when a dose appropriate to a normal child of the same age was given, the time of fall to a normal fasting blood-sugar level was increased. This curve closely resembles many of those given by Ross (1936). It seems evident that the 'impaired tolerance' which Ross reports in his coeliac patients is in fact the result of a relatively greater dosage of glucose as compared with normal subjects. The same explanation is applicable to similar findings reported by Fairley (1936) in cases of tropical sprue. Thaysen (1929 *a*, 1932), in contrast to Ross, observed an increased tolerance to intravenous glucose in three out of six cases of idiopathic steatorrhoea which he investigated, using the technique devised by Jorgensen and Plum (Jorgensen and Plum, 1922; Jorgensen, 1926). The remaining cases gave normal results. The reason for the difference between Thaysen's results and those of the present investigation is not evident; it is noteworthy, however, that Thaysen examined no normal series of his own, but compared his results with the normal series reported by Jorgensen. While differences of technique prevent direct comparison with the normal curves in this study, Jorgensen's normal curves appear to lie within narrower limits than experience here has indicated.

The Response to Insulin in Coeliac Disease

The reaction of the blood-sugar level to insulin injections has been used as a test of the normality of the carbohydrate metabolism of patients with coeliac disease. Badenoch and Morris (1936), using a subcutaneous injection of 4 units, obtained a fall in the blood-sugar level greater than they found in normal subjects of the same age, and they suggest that in coeliac disease there is a deficiency of some contra-insular hormone. On the other hand, Ross (1936), using an intravenous injection of 4 units of crystalline insulin, found a smaller depression of the blood-sugar level in coeliac than in normal children. A similar curve to that found in coeliac disease was obtained from normal children when the test was performed after a period on a low carbohydrate diet. Ross interpreted his findings as indicating again that the patient with coeliac disease was, in respect of carbohydrate, in the same condition as a normal subject starved of carbohydrate. Carbohydrate, while present in the diet, was not being absorbed. The effect of intravenously injected crystalline insulin on the blood-sugar level has been studied in six of the cases of coeliac disease in the present series, and has been compared with the results from six normal children. A dosage of one-third of a unit of insulin per kg. of body-weight was employed, and the blood-sugar was estimated before the injection and at ten-minute intervals thereafter for one hour.

The results of these insulin sensitivity tests are detailed in Table V. They show that the time and extent of the maximum response to insulin

vary considerably amongst the normal subjects, and that a similar variability occurs amongst the coeliac cases. From the figures it seems clear that there is no significant difference between the two groups in their response to insulin. The normality of the insulin sensitivity tests in the present series of cases of coeliac disease provides further corroborative evidence that in coeliac disease there is no disturbance of the intermediate carbohydrate metabolism.

TABLE V

Insulin Sensitivity Tests in Normal Subjects and in Cases of Coeliac Disease.
(1/3 unit insulin per kg. body-weight intravenously.)

| Time. | Normal subjects. | | | | | | | Cases of coeliac disease. | | | | | | |
|------------|------------------|----|----|----|----|----|-------|---------------------------|----|----|----|----|----|-------|
| | 1 | 2 | 3 | 4 | 5 | 6 | Mean. | 1 | 2 | 3 | 4 | 7 | 8 | Mean. |
| Fasting | 76 | 96 | 70 | 79 | 93 | 90 | 84 | 72 | 68 | 98 | 95 | 90 | 66 | 81 |
| 10 minutes | 68 | 66 | 52 | 66 | 88 | 55 | 66 | 61 | 50 | 48 | 61 | 77 | 43 | 56 |
| 20 " | 59 | 38 | 24 | 48 | 75 | 56 | 50 | 57 | 32 | 45 | 41 | 61 | 31 | 44 |
| 30 " | 50 | 40 | 39 | 50 | 57 | 54 | 48 | 61 | 41 | 45 | 67 | 56 | 32 | 50 |
| 40 " | 54 | 64 | 45 | 57 | 68 | 65 | 59 | 47 | 47 | 50 | 70 | 54 | 56 | 54 |
| 50 " | 45 | 52 | 65 | 70 | 54 | 67 | 59 | 47 | 52 | 52 | 68 | 54 | 72 | 57 |
| 60 " | 54 | 57 | 63 | 68 | 66 | 69 | 63 | 48 | 52 | 57 | 70 | 48 | 72 | 58 |

Summary

1. The *intravenous* glucose tolerance test has been carried out on 12 cases of coeliac disease, 11 of whom showed a typical low *oral* blood-sugar curve. No significant difference was found between the curves from the coeliac patients and curves from normal subjects; and in five of the patients no difference was observed between curves obtained during active and latent phases of the disease.

2. Insulin sensitivity tests on six of the patients gave results closely similar to those obtained from six normal subjects.

3. From these results it is concluded that there is no abnormality of intermediate carbohydrate metabolism in patients with coeliac disease; and, by exclusion, it seems certain that the low blood-sugar curve of coeliac disease must be due to delayed or defective absorption of carbohydrate from the bowel. This conclusion is presumably applicable to other forms of idiopathic steatorrhoea as well as to coeliac disease.

I have pleasure in expressing my indebtedness to Professor G. B. Fleming for his valuable criticism and advice, and to the clinical and biochemical staffs at the Hospital for the assistance which they have given. Part of the expenses of this work were defrayed by a grant from the Medical Research Council.

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RHEUMATIC HEART DISEASE AS MET WITH IN HOSPITAL PRACTICE IN CEYLON¹

By P. B. FERNANDO

(From the General Hospital, Colombo)

With Plate 18

Introduction

CONFLICTING views have been expressed on the subject of the occurrence of rheumatic fever and carditis in the tropics. One set of authorities is definite that rheumatic infection hardly ever occurs in the tropics, another, while admitting that genuine cases are occasionally seen in the tropics, thinks that the incidence is very low, the manifestations very mild, and the sequelae less virulent. Lastly, there are others who maintain that the incidence, manifestations, and sequelae scarcely differ from what is seen in Europe. Recently, Stott (1938) has reviewed the literature on the subject and thrown considerable light on the prevalence of rheumatic carditis in India.

The present paper records the results of two studies :

(a) The autopsy records of the General Hospital, Colombo, for the period July 1934 to November 1937, have been studied for evidence of rheumatic carditis.

(b) A clinical study has been made for evidence of rheumatic infection among the case records of the patients admitted to the wards at the General Hospital, Colombo, under the care of the author during the same period.

The post-mortem examinations were carried out by the Pathologists to the Hospital, and the material came from the wards of all the members of the visiting staff. As such the findings are indicative of the incidence, &c., for the whole hospital.

The clinical study, however, was confined to the author's own cases and has the advantage that one person was responsible for the clinical observations and notes. Even here the findings may be taken as fairly representative of conditions that prevail in the whole hospital, as the cardiovascular admissions are evenly distributed among the six physicians of the hospital, and no selection is made. As Ceylon is typically a tropical country, it is hoped that the results of this combined study may be of use to those engaged in the study of rheumatic infection in the tropics.

¹ Received May 5, 1939.

Post-mortem Series

During the period under review 1,110 post-mortem examinations were performed at the General Hospital, Colombo, exclusive of those done by the Judicial Medical Officer. In 178 of these there was evidence of cardiovascular disease, and 41 of these were cases of rheumatic carditis, distributed as follows :

Rheumatic carditis :

1. Valvular lesions :

| | |
|--|----|
| Mitral stenosis | 27 |
| Mitral regurgitation | 2 |
| Mitral stenosis and aortic regurgitation | 5 |
| Mitral stenosis and aortic stenosis | 3 |
| Pure aortic stenosis | 1 |

38

2. Pericarditis 3

Total 41

The percentage incidence was as follows :

| Nature of lesions | Number. | Total cardio-vascular cases. | Percentage of cardio-vascular cases. | Total post-mortem exams. | Percentage of total post-mortem exams. |
|------------------------------|---------|------------------------------|--------------------------------------|--------------------------|--|
| 1. Pure mitral lesions | 29 | 178 | 16.3 | 1,110 | 2.6 |
| 2. Mitral and aortic lesions | 8 | " | 4.5 | " | 0.72 |
| 3. Pure aortic lesions | 1 | " | 0.56 | " | 0.09 |
| 4. Pericarditis | 3 | " | 1.68 | " | 0.27 |
| Total | 41 | 178 | 23 | 1,110 | 3.6 |
| (a) Mitral lesions | 37 | 178 | 20.8 | 1,110 | 3.3 |
| (b) Aortic lesions | 9 | " | 5.1 | " | 0.8 |

It will be seen that rheumatic carditis accounted for 23 per cent. of the cardiovascular autopsies, and 3.6 per cent. of the total. Of these cases of rheumatic carditis, valvular lesions were present in 92.7 per cent., and the mitral valve was affected in every case save one in which there was pure aortic stenosis. In four of these cases aortic stenosis was found in association with mitral stenosis. In five cases there was aortic incompetence associated with mitral stenosis. The mitral valve was affected four times as often as the aortic valve. The proportion of pure mitral lesions to pure aortic valvular lesions was 29 : 1. Where the aortic valve was involved, incompetence was present in five cases, while there was stenosis in four cases. In the whole series there was one other case of aortic stenosis, and this was in an old patient and probably of the degenerative type. In one case there was rheumatic endocarditis of both mitral and tricuspid valves. The involvement of the left heart was therefore thirty-eight times commoner than that of the right heart.

The age and sex distribution was as follows :

| Age in years. | Male. | Female. |
|----------------|-------|---------|
| 0 to 10 | 0 | 0 |
| 11 to 20 | 3 | 7 |
| 21 to 30 | 6 | 7 |
| 31 to 40 | 5 | 3 |
| 41 to 50 | 3 | 1 |
| 51 to 60 | 2 | 2 |
| Age not stated | 2 | 0 |
| | 21 | 20 |

The proportion of males to females in the whole post-mortem series was 69 : 31, and it was about the same in the cardiovascular cases. In the cases of rheumatic carditis it was 21 : 20. This demonstrates the greater frequency of rheumatic carditis in females. This incidence is in striking contrast to the figures for cardiovascular syphilis in this series, where the proportion of males to females was 15 : 1.

The percentage distribution of deaths in each group was as follows :

| Decade. | Percentage of total deaths. |
|----------------|-----------------------------|
| 11 to 20 years | 25.5 |
| 21 to 30 " | 33.3 |
| 31 to 40 " | 20 |
| 41 to 50 " | 10 |
| 51 to 60 " | 10 |

A little less than 60 per cent. of the deaths, therefore, were in subjects below the age of 30 years, and nearly 80 per cent. in subjects below the age of 40 years. According to Lewis (1933) the mortality in the first year after the onset of rheumatic infection is about 5 per cent. ; and it is 20 per cent. in the first ten years. In the present series it is neither known when the infection first set in nor what proportion these post-mortem cases bear to the clinical admissions ; also children under 8 years of age are not admitted into this hospital except in exceptional cases. Nevertheless, as there were 10 cases below the age of 20 years, and as five of these were below the age of 15 years, the rate of progress of rheumatic carditis does not seem to be any less rapid in Ceylon than in temperate climates.

Pathological features. 1. *Pericarditis.* In addition to three cases of uncomplicated pericarditis, there were five other cases where there was macroscopic evidence of rheumatic pericarditis in addition to valvular lesions.

2. *Association with congenital lesions.* There were three cases of congenital heart lesions co-existing with mitral stenosis. One was a case of patent interventricular septum, and two were cases of patent foramen ovale.

3. *Recent endocarditis.* In four cases there was evidence of recent endocarditis in addition to the more chronic valvular lesions. One was in a patient aged 35 years and another 45 years. Unfortunately the age was not recorded in the other two. In one case there was no chronic valvular lesion, but only recent endocarditis of the mitral valve. The patient was aged 10 years, a female ; the heart was enlarged, the muscle pale and flabby, and the right heart distended. The histological note states : ' typical Aschoff bodies '.

4. *Mural endocarditis.* Evidence of healed endocarditis of the left auricle was found in two cases of mitral stenosis. Attention has been drawn to this condition by MacCallum and Von Glahn (quoted by Boyd, 1935).

5. *Degree of valvular deformity.* There was marked stenosis of the mitral valve in seven cases, in one the notes stating that 'the valvular opening was almost closed'. In two other cases there was severe mitral stenosis, associated with severe aortic stenosis. The notes in these cases may be quoted as illustrating the series.

Female aged 25 years. 'Marked hypertrophy of heart with dilatation of the right side. Extreme stenosis of the aortic orifice, the valves are about 4 mm. thick and adherent, leaving an orifice of about 4 mm. in diameter. Mitral orifice is stenosed, valves are thickened and the orifice slitlike. Chordae tendineae are short and thickened.'

Male aged 30 years. 'Aortic valves sclerosed, there is stenosis; admits index finger. Mitral orifice stenosed, admits only tip of finger.'

In the rest of the cases stenosis was moderate with sclerosis of valves, thickening and shortening of chordae tendineae. Photomicrographs of sections showing Aschoff nodules are shown in Plate 18, Fig. 1,

Proportion of rheumatic valvular lesions to other valvular lesions. The following table demonstrates the relationship of the incidence of rheumatic valvular lesions to valvular lesions due to other causes.

| | Pure aortic. | Pure mitral. | Mixed aortic and mitral. | Total. | Percentage of total. |
|-----------------------------------|-----------------|-----------------|-----------------------------|--------|-------------------------|
| Rheumatic | 1 | 29 | 8 | 38 | 56.7 |
| Syphilitic | 6 | 0 | 0 | 6 | 9 |
| Bacterial endocarditis | 2 | 5 | 3 | 10 | 14.9 |
| Degenerative (atherosclerosis) | 3 | 8 | 2 | 13 | 19.4 |
| Total | 12 | 42 | 13 | 67 | — |
| Percentages of total | 18 | 62.7 | 19.4 | — | 100 |

Syphilis caused only aortic valvular lesions, in every case incompetence of the valve, causing aortic regurgitation and enlargement of the left ventricle with hypertrophy. In two cases there was aneurysm of the aorta as well. Bacterial endocarditis was easily recognized by the nature of the vegetations. Here again the mitral valve was involved more often than the aortic valve. Under the term '*degenerative*' is included one case of pure aortic stenosis in a patient of 72 years, in whom there was no evidence of mitral stenosis. The others are examples of the condition which has been described as *atherosclerotic heart disease*. In this condition there is slight sclerosis of the endocardium of the valves as well as of the chambers. It is, as a rule, found in elderly patients with chronic nephritis and is of no clinical importance. The condition is important from the pathological point of view, as it might be mistaken for the lesions produced by infectious conditions (Sprague and White, 1935). In this series eight of the patients were over 45 years of age, and had atheroma of the aorta and coronary vessels, and granular kidneys; in four, where the age was less than 45 years, there was evidence of secondary contracted kidney.

Comparison with other countries. The following table compares the post-mortem incidence of rheumatic heart disease in certain hospitals in London and Bombay with that of the General Hospital, Colombo. It will be seen that the percentage of rheumatic cases of the total cardiovascular autopsies is similar in the three countries. The percentage of rheumatic fever cases of the total autopsies is also similar in the case of the London and Colombo hospitals, but in Bombay there is apparently a greater incidence of other fatal diseases. Thus, while cardiovascular disease accounts for 14.4 per cent. of the London autopsies, and 16 per cent. of the Colombo autopsies, in Bombay it is only 7 per cent.

| | London: Guy's and St. Mary's.† | Bombay.† | Colombo. |
|---|-----------------------------------|----------|----------|
| 1. Rheumatic heart disease (post-mortem examinations) | 162 | 47 | 41 |
| 2. Total cardiovascular (post-mortem examinations) | 631 | 176 | 178 |
| 3. Total post-mortem examinations | 4,378 | 2,498 | 1,110* |
| 4. Percentage of rheumatic cases (1+2) of total vascular post-mortem examinations | 25 | 27 | 23 |
| Percentage of rheumatic cases of total post-mortem examinations | 4 | 2 | 3.6 |

* Includes all post-mortem examinations, including tropical diseases.

† Stott (1938).

Conclusions. 1. The post-mortem incidence of rheumatic carditis appears to be the same in Colombo General Hospital as in Guy's and St. Mary's Hospitals, London.

2. The mitral valve was the one most frequently affected (92.7 per cent.).

3. The aortic valve was affected less often, and almost always in association with lesions of the mitral valve.

4. Pure aortic lesions were rare compared with pure mitral lesions, the proportions being one of the former to 29 of the latter.

5. Aortic stenosis was almost as common as aortic incompetence, a finding different from that which is experienced elsewhere.

6. Severe degrees of mitral stenosis were found in nearly one-fourth of the cases.

7. Females were comparatively more susceptible to rheumatic carditis than males. Pure mitral lesions were commoner in females than in males, while mixed mitral and aortic lesions were commoner in males.

8. A quarter of the deaths were in patients below the age of 20 years and nearly 60 per cent. in patients below the age of 30 years.

9. The incidence, manifestations, virulence, and progressiveness of the disease seem to be very little different from what they are in temperate climates.

Clinical Series

During the period under review 657 patients were admitted with evidence of disease of the cardiovascular system. The total admissions were 10,003,

of which 3,531 were for malaria. The figures for malaria were abnormal and were due to the great malaria epidemic which occurred in the early part of this period. In normal times malaria admissions would not have exceeded one-tenth of this number. If the excess malaria cases are excluded, the incidence of the cardiovascular cases in these wards will be approximately 10 per cent. of the total admissions. In 143 of the 657 there was evidence of rheumatic carditis, giving a case incidence of 21.5 per cent. of cardiovascular admissions and 1.4 per cent. of total admissions. In addition to the above there were 71 patients with rheumatic arthritis and one with chorea, but in whom there was no evidence of carditis. The incidence of rheumatic infection in the series was therefore 2.2 per cent. of the total admissions.

The cases were classified as follows :

| | |
|--|-------|
| Mitral valvular disease alone | 101 |
| Mitral and aortic disease combined | 12 |
| Aortic disease alone | 2 |
| Pericarditis | 10 |
| Auricular fibrillation alone | 7 |
| Acute carditis of recent onset | 11 |
| Chorea alone | 1 |
| Rheumatic arthritis alone | 71 |
| | <hr/> |
| | 215 |

The diagnosis was made in every case on clinical grounds. Mitral stenosis was diagnosed in the presence of a persistent diastolic mitral murmur. A persistent systolic murmur, the murmur conducted outwards, in patients with a rheumatic history was the evidence for mitral regurgitation. Aortic regurgitation was diagnosed in the presence of an aortic diastolic murmur conducted downwards, either to the mitral area or along the left border of the sternum. A high pulse-pressure, collapsing pulse, 'femoral thud', capillary pulsation, and cardiac enlargement, especially of the left ventricle, were found in all marked cases. Pericarditis was diagnosed where there was a pericardial friction rub, or enlargement of the area of cardiac dullness with its characteristic shape, or both. Rheumatic carditis of recent onset was diagnosed in those cases of rheumatic arthritis where there was cardiac enlargement or mitral murmurs, but which lacked the characteristics of the murmurs associated with the fully developed lesions.

In many of the cases it was possible to supplement the clinical evidence with X-ray examination and electrocardiograms. In pericarditis not only was the shape of the heart shadow characteristic, but direct observation under the fluorescent screen enabled one to distinguish between the limits of fluid and of the heart. No orthodiagraph was available, but in the ordinary X-ray plate the 'boot-shaped' heart of aortic regurgitation with its accentuation of the normal concavity between the descending aortic arch and the left ventricle was as easily distinguished as the characteristic shape of the heart in mitral stenosis, where the normal concavity was converted into a convexity by the enlargement of the left auricle and right

ventricle. The filling in of the posterior mediastinum and displacement of the oesophagus in mitral stenosis was also observed in some cases by X-ray screening. The diagnosis of auricular fibrillation or flutter was, as a rule, confirmed by electrocardiograms. Several possible sources of error were constantly kept in mind before a diagnosis of rheumatic carditis was made. A mitral diastolic murmur has been described in cases of ankylostomiasis (Gunewardene, 1933). There was no difficulty in distinguishing it from the diastolic murmur of true organic stenosis. While the latter was persistent and often progressive, the former was never well marked, was only found very occasionally, and that in association with anaemia and cardiac enlargement, and it quickly disappeared with treatment for these two conditions. Occasionally gonorrhoeal arthritis may resemble rheumatic arthritis. This condition was excluded by careful attention to the history, clinical signs and symptoms, and in some cases with the additional help of appropriate tests such as complement fixation tests, examination of prostatic or cervical smears for gonococci, blood culture, &c. Lastly, in several cases the clinical diagnosis was verified by necropsy.

Rheumatic arthritis. Ninety-three patients were admitted for arthritis. The usual history was that pain and swelling appeared suddenly in one or more joints, with a rise of temperature. After a few days of native treatment the pain and swelling disappeared only to reappear in other joints. These, again, healed in a few days and the patient was able to get about his business for a couple of weeks, when he got a relapse. In other cases improvement had never been complete, the arthritis flitting from joint to joint, attacking new joints, reappearing in those already cured, and incapacitating the patient for weeks. As a rule the arthritis was more severe and tended to be more persistent in adults than in children and adolescents, but there were many exceptions to this rule. Suppuration was never noted in any case; healing was complete and left no deformity. In a few cases where arthritis had recurred again and again recovery was delayed for a couple of weeks, and some degree of stiffness left for some time. Ankylosis never resulted in any case.

The arthritis was multiple in over four-fifths of the cases. Of the joints affected, the greatest frequency was in the knee. This was affected in 54 patients, in 14 of whom it was bilateral. The ankle came next and was inflamed in 45 patients, in 12 the inflammation being bilateral. The wrist came third with 26, and the elbow fourth with 16 cases. The tendency for bilateral involvement was distinctly less in these two joints. The remaining joints were affected in the following order of frequency (the figures indicate the number of times they were affected): small joints of the foot 9, shoulder 5, hip 5, small joints of the hand 4, neck 3, sternoclavicular joint 1, and mandible 1.

As in rheumatic arthritis of temperate climates, there was a ready response to treatment with salicylates. There was hardly any case where the pain, swelling, and temperature did not respond to full doses of this drug.

The most important point of resemblance to rheumatic infection of temperate climates was the nature and frequency of cardiac involvement. In 22 of the 93 patients there was evidence of carditis. In half of this number it was of the nature of chronic valvular disease, mitral stenosis being found in every case, while in one there was aortic regurgitation as well. In the remainder the carditis was of a more recent onset and was manifested by a systolic murmur in eight, a diastolic murmur in one, and distinct cardiac enlargement as ascertained by percussion in two cases.

Inquiry into the previous history of these patients gave useful information. The patients with chronic valvular disease and acute arthritis all gave a history of previous attacks of arthritis. They had all had several attacks spread over a number of years. Two of them had also had cerebral embolism producing hemiplegia. On the other hand, in only two of the patients with acute carditis was there a previous history of rheumatic fever; in one it was eight years previously and in the other five years. The rest were cases of recent infection, the average duration of the illness previous to infection being about one month. Six of these latter were under 20 years of age. Among those with arthritis, but no evidence of carditis, 22 gave a previous history of arthritis.

Subcutaneous rheumatic nodules. In temperate climates subcutaneous rheumatic nodules occur in about a tenth of the cases (Lewis, 1933) and they are almost confined to children (Price, 1930). Although carefully looked for, rheumatic nodules were not found in any of the patients in this series. This may be partly due to the fact that there were only nine patients below 10 years of age. Nevertheless, it is the general opinion that rheumatic nodules are rare in Ceylon.

Rheumatic carditis. Although rheumatic infection, when it affects the heart, produces a pancarditis, all the structures are seldom affected equally. Clinically the cases fall into various groups and are commonly described for convenience according to the predominating lesion. In the present series this feature was also observed. There were cases where the main picture was that of valvular disease, in others it was that of pericarditis, and in yet others the only manifestations of carditis were auricular fibrillation and congestive failure. In those cases which came to autopsy it was, however, found that evidence of disease was not confined to one structure.

Valvular disease (chronic). Chronic valvular lesions were diagnosed in 115 patients. In 113 of these there was evidence of mitral disease and in 14 evidence of aortic disease, including 12 cases where there was mixed mitral and aortic disease. Thus mitral lesions were eight times as numerous as aortic lesions and formed 98.2 per cent. of the series. Uncomplicated aortic lesions were rare compared with uncomplicated mitral lesions, the latter being 50 times as numerous as the former. A previous history of rheumatic arthritis was found in 38 of the patients with chronic valvular disease, and in 11 of these there was arthritis in addition at the time of stay in hospital. Congestive heart failure, as shown by oedema of legs, enlargement of liver, distended veins in

the neck, &c., was found in 68 of the 115 patients. Three patients with mitral stenosis developed auricular flutter, while there were 13 cases of auricular fibrillation in association with mitral stenosis; in no case of aortic regurgitation was this disturbance noted. Thirty-three patients died in hospital during this period, 20 of whom had congestive failure, and five congestive failure with auricular fibrillation. One died of an intercurrent attack of pneumonia, one developed subacute bacterial endocarditis (confirmed by autopsy), and of the other two one had a cerebral embolism and one auricular fibrillation. The mortality rate, therefore, of the valvular lesions was 28.7 per cent., and congestive failure was the commonest antecedent to a fatal termination.

Pericarditis. There were 10 patients in whom there was clinically evident rheumatic pericarditis. Six of these patients had congestive cardiac failure. Four of the patients died in hospital, and of these, two had signs of congestive failure. Pericarditis formed 6.9 per cent. of the cases of rheumatic carditis, and this is similar to the incidence in the post-mortem series, which was 7.3 per cent.

Disturbances of rate and rhythm. Tachycardia was a common feature and was met with in nearly all the cases. Extrasystoles were met with on occasions in many of the patients with chronic valvular lesions, but required no attention. In two patients, aged 40 and 44 years, with mitral stenosis, they were persistent. Partial heart-block was found in one case. Auricular flutter was found in three patients with mitral stenosis. The commonest abnormality of importance met with was auricular fibrillation. This was found both in patients with mitral stenosis and in those who showed no evidence of valvular disease. There were 13 of the former and seven of the latter. There were altogether 22 cases in the whole series, 20 of which were rheumatic in origin and two arteriosclerotic. According to Lewis (1933), two-thirds of cases of auricular fibrillation belong to the rheumatic group. There were no cases of auricular fibrillation due to thyrotoxicosis. Nearly a quarter of the patients above the age of 30 years with rheumatic carditis had auricular fibrillation, while in those under 30 the percentage incidence was only 6.1 per cent. This is in accordance with the experience in temperate climates.

Chorea. There were three patients with chorea in the series, all female. Two of them had mitral stenosis. The third case was a young woman aged 19 years who gave no history of rheumatic fever and whose heart was normal. The patient was removed after two days in hospital for treatment by an exorcist. The manifestations of chorea in these three cases were typical of the condition, and were characterized by agitation and extreme fidgetiness, irregular, purposeless, non-repeated movements of the hands and legs, grimaces of the face, weakness and hypotonicity of muscles, inability to keep the tongue protruded without gripping it between the teeth, &c. The incidence of chorea in this series is certainly very much less than in other countries, but it is possible that most of these cases are not admitted into

hospital, but taken to exorcists, as the popular view is that the patient is possessed by a devil, and the appropriate treatment is not medical but magical.

Relationship between rheumatic arthritis and carditis. (a) Of the 215 patients with rheumatic infection, 143 had cardiac lesions and 72 were without any evidence of cardiac involvement.

(b) Of the 143 with carditis, 50 patients gave a history of previous attacks of rheumatic arthritis, and 11 of these had acute arthritis at the time of stay in hospital also. Another 11 had had no previous attacks, but had both carditis and arthritis at the time of examination.

(c) Eighty-two patients with carditis gave no history of arthritis, past or present.

It is interesting to compare these figures with those of countries where rheumatic infections are well known to occur. The following table gives a comparison of certain relevant figures for Australia and Ceylon. The Australian figures are the average annual numbers for the five general hospitals in Victoria (Graham, 1937); the Ceylon figures are from this series.

| | Total rheumatic patients. | Rheumatic fever alone. | Percentage. | Chorea. | Percentage. | Carditis. | Percentage. | Deaths. | Mortality of cases per cent. |
|-----------|---------------------------------|---------------------------|-------------|---------|-------------|-----------|-------------|---------|------------------------------------|
| Australia | 251 | 67 | 26 | 9 | 3.6 | 175 | 70 | 51 | 29 |
| Ceylon | 215 | 71 | 33 | 3* | 1.4 | 143 | 66.5 | 38 | 26.5 |

* Including two cases with mitral stenosis counted above.

The incidence of rheumatic infections to total admissions, including surgical cases, in the Australian series was 1.2 per cent. The ratio to medical admissions only in the Ceylon series was 2.2 per cent. There is thus a close correspondence in the figures for the two countries. With regard to rheumatic history, even in England where the importance of rheumatic fever and the part it plays in producing heart disease are thoroughly recognized, a history of rheumatic fever is frequently missing in patients who attend hospital with cardiac lesions. According to a report of the London County Council, half of the cases of serious heart disease gave no preceding history of recognizable illness, except vague ill-health, tenderness, and pallor (Clarke, 1932). The absence of a history of rheumatic arthritis in 57 per cent. of the cases of rheumatic carditis in the Ceylon series is not very much different from experience in temperate climates.

Age incidence. Over four-fifths of the cases (83.2 per cent.) and of the deaths (81.6 per cent.) occurred in patients in the age groups 1 to 40 years. In the post-mortem series nearly 80 per cent. of the autopsies were in subjects of the same age groups. The heaviest incidence in most of the conditions was in the two age groups 21 to 40, being 44.5 per cent. for mitral disease, 71.4 per cent. for aortic disease, 50 per cent. for pericarditis, and 57.7 per cent. for rheumatic arthritis. Acute carditis, however, was commoner at a younger age (81.1 per cent. of the cases being in age group 11 to 30) and

auricular fibrillation at an older age (60 per cent. being in age groups 31 to 50 years). The above figures show that in Ceylon also rheumatic carditis is a disease of adolescence and early adult life, and that the majority of patients so affected die before they reach the age of 40 years.

Racial incidence and economic status. The following table gives the racial incidence of cases in the series, as well as the approximate percentage figures for the racial distribution of the population in (a) Ceylon, (b) Western Province, (c) Colombo (Registrar General's report, 1937; Ceylon Census, 1921).

| Race. | Cases. | Percentage. | Percentage of the races in the general population of: | | |
|---------------|--------|-------------|---|-------------------|----------|
| | | | Ceylon. | Western Province. | Colombo. |
| Singhalese | 177 | 82.3 | 67 | 81.8 | 45 |
| Ceylon Tamils | 14 | 6.5 | 24.9 | 9.3 | 23 |
| Indian Tamils | 8 | 3.7 | | | |
| Burghers | 9 | 4.2 | 0.7 | 1.5 | 5.9 |
| Muslims | 7 | 3.3 | 6.6 | 5.9 | 18 |
| Europeans | None | 0 | 0.2 | 0.3 | 1.1 |

The different races are not uniformly distributed throughout the country. The Ceylon Tamils preponderate in the northern and eastern parts of the island, and the Indian Tamils are mostly found in the central parts of the island on the tea and rubber plantations. In the western and southern parts of the island the Singhalese are in the majority. The Burghers are usually found in towns, mainly Colombo. Although patients from all parts of the island seek treatment at the General Hospital, Colombo, those from the Western Province predominate. Hence the population figures for the Western Province may be taken as those representing the distribution of the different races in the community at large which is served by the General Hospital, Colombo. It will be seen that the racial incidence of the rheumatic infections in this series follows closely the racial incidence in the population of the Western Province. There is, apparently, no greater susceptibility in any particular race, except one, to the development of rheumatic infections. The Burghers, judging from the percentage incidence of cases in this series when compared with their numbers in the population, appear to be more susceptible. This increased susceptibility may be, however, more apparent than real, because as a rule they do not resort to native medicine, as the other races do. A relatively larger proportion of their population seek hospital treatment. All the patients, except the Indian Tamils who come from South India, belonged to the indigenous population and had never been out of Ceylon.

All the patients in this series were in the non-paying section of the hospital, and were presumably not able to pay for medical aid. The great majority of them were of the poorer classes—labourers, peasants, domestic servants, artisans, &c. A small percentage belonged to the lower middle class. It has been found (Nicholls, 1936) that malnutrition is widespread in this class of patients, and that their diet is deficient both in quality and quantity when compared with that of the upper classes. The incidence of rheumatic

carditis seems to vary with the social and economic level of the population. The incidence given above is that among the non-paying hospital classes. Other workers, too, have found rheumatic infections quite prevalent among this class of patients in Ceylon. Fernando (1934), from his experience as an out-patient physician of the General Hospital, Colombo, at that time, says that the clinical picture of rheumatic fever is almost identical with that seen in Europe, and that cardiac complications are the commonest conditions associated with the disease. He reports a study of 40 cases personally seen by him in one year. Wijerama (quoted by Gunewardene, 1935) found that mitral stenosis and regurgitation accounted for 20 per cent. of the cardiovascular cases in the non-paying section of the General Hospital, Colombo, in the year 1932. There were also 63 cases of rheumatic fever in the same year. On the other hand, Gunewardene found in private consulting practice among the upper classes that mitral stenosis and regurgitation accounted for only 8 per cent., and rheumatic fever 5 per cent. of 400 cardiac patients seen by him. Moreover, in this class of patients the disease apparently ran a mild course. This variation in incidence in different strata of society is also found in other countries. In England rheumatic fever is found particularly amongst the overcrowded and poorer parts of the population of towns (Lewis, 1933). In Victoria, Australia, where rheumatic infections accounted annually for 1.23 per cent. of total admissions and 2.03 per cent. of total deaths in the general hospitals, 2.5 per cent. of total admissions and 1.7 per cent. of the total deaths in children's hospitals, and 3 per cent. of total autopsies in a children's hospital, it was estimated that the private practitioners, as a whole, do not on an average see more than one rheumatic patient per annum. Even this estimate was considered by some practitioners as too high (Melbourne Paediatric Society, 1937).

Physiography and climatic conditions of Ceylon (Ceylon Sessional Paper, 1935). *Physiography.* Ceylon lies between 5° 55' and 9° 50' North latitude. It is 25,332 square miles in area, its greatest length being 270 miles and its greatest breadth 140 miles. The greater part of the island is low-lying and flat; the northern and north-central parts form one great plain stretching from sea to sea, and farther south the maritime districts consist of similar level or undulating stretches, but the south-central part of the island is occupied by a mass of hills and mountains, some of whose peaks reach a height of 7,000 ft. or more. Ceylon is a relatively well-watered country with numerous rivers and streams.

Climate. In the low plains temperature and humidity are comparatively uniform, but rainfall varies considerably in different parts of the country. Along the coast the annual mean temperature is about 80° F., and a noteworthy feature is the smallness of the variation both between day and night in the same 24 hours and between the different parts of the year. At Kandy, 1,654 ft. above sea-level, the mean temperature is 76.7° F., and the formula of 1° drop in temperature for each 300 ft. rise in altitude holds fairly well throughout the island. Everywhere in Ceylon there is a relatively

high degree of humidity; the average percentage varies little from month to month. During the south-west monsoon the relative humidity by day is usually well over 70 per cent. in the wet zone, and at night, owing to the fall in temperature, it is about 90 per cent. Even in dry zones the average humidity in any month rarely falls below 60 per cent. Ceylon may be divided into a wet zone and a dry zone. The former covers the south-west quadrant of Ceylon, the coastal plain as well as much of the hill country. Over most of this zone the average annual rainfall is more than 100 in., and in places reaches 200 in. In the dry zone the average rainfall is less than 75 in. per annum, and there are large tracts with annual averages of less than 40 in.

Summary of Clinical Findings

1. The incidence of rheumatic infections was 2.2 per cent. of the total admissions. The incidence of rheumatic carditis was 1.4 per cent. of the total admissions and 21.5 per cent. of cardiovascular admissions. Approximately one-third of the rheumatic cases had no evidence of carditis, while two-thirds had evidence of carditis. The above figures agree closely with similar figures for the five general hospitals in Victoria, Australia.

2. The clinical manifestations of rheumatic arthritis were in no way different from those of the conditions diagnosed as such in temperate climates.

3. The tendency to the occurrence of carditis was similar. Adolescents and young adults were those most liable; the manifestations of the carditis were also similar. Valvular lesions predominated as in other countries.

4. The commonest valvular lesion was mitral stenosis, and next in order of frequency came aortic regurgitation. Mitral lesions were eight times as numerous as aortic lesions.

5. Clinically evident pericarditis occurred in 6.9 per cent. of the cases of rheumatic carditis.

6. Auricular fibrillation occurred in nearly a quarter of the patients above the age of 30 years who showed evidence of carditis. About two-thirds of the cases of auricular fibrillation were in patients with mitral stenosis. Auricular flutter was found in three cases of mitral stenosis. Auricular fibrillation and flutter therefore occurred in 16 per cent. of all the cases of rheumatic carditis.

7. Uncomplicated rheumatic arthritis was commoner in males than in females, but carditis both in the acute and chronic forms occurred more frequently in the female.

8. Over four-fifths, both of the cases and of the deaths, were in patients below 41 years of age. The heaviest incidence was in the two age groups between 21 and 40 years. The above figures show that in Ceylon also rheumatic carditis is a disease of adolescence and early adult life, and the majority of patients so affected die before they reach the age of 40 years.

9. There was no greater susceptibility to rheumatic infection in any one of the races inhabiting the island.

10. All the cases studied were in the poorer classes of the population, and factors common to all were over-crowding and malnutrition.

11. The incidence of chorea in this series was only one-third of that in Victoria, Australia.

12. Subcutaneous rheumatic nodules were not met with; they are supposed to be rare in Ceylon.

Summary and General Conclusions

1. The autopsy records of the General Hospital, Colombo, for the period July 1934 to November 1937 have been studied for evidence of rheumatic carditis.

2. The records of 215 patients admitted for rheumatic infections into the wards at the General Hospital, Colombo, under the care of the author during the same period, have been studied from the clinical point of view.

3. The conclusions from the clinical study are in agreement with those derived from the study of autopsy records.

4. Rheumatic infection is an important cause of heart disease among the hospital classes of the population of Ceylon, and accounts for anything between one-fourth and one-fifth of the total cardiovascular disease among them.

5. The incidence, manifestations, virulence, and progressiveness of rheumatic carditis scarcely differ in any important respects from what is seen in non-tropical countries.

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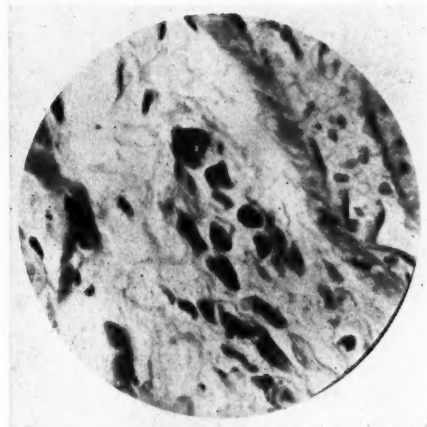
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Magnification $\times 285$



Magnification $\times 575$

FIG. 1

Sections showing an Aschoff nodule under different magnifications from the heart of a male patient aged 14 years, admitted for dyspnoea and palpitation.

Heart much enlarged, systolic and diastolic murmurs heard over mitral area. Liver enlarged; neck veins distended. History of several attacks of painful swelling of ankle- and knee-joints during the preceding seven months. *Post mortem*:—heart enlarged, 482 gm. weight. Right auricle and right ventricle showed dilatation and hypertrophy. Left auricle hypertrophied and dilated; the mitral orifice was stenosed and just admitted a pencil. The chordae tendineae of the left ventricle were shortened and thick



FIG. 2. E. P. Male, aged 14 years. Rheumatic carditis

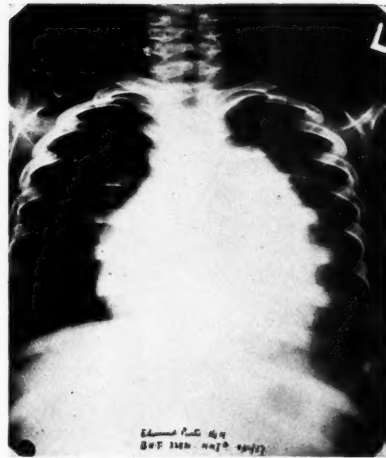


FIG. 3. X-Ray: Antero-posterior view of heart showing enlargement of right side of heart and left auricle

SIMMONDS'S DISEASE DUE TO POST-PARTUM NECROSIS OF THE ANTERIOR PITUITARY¹

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Introduction

DURING the past few years the term 'Simmonds's disease' has undergone a gradual change in significance. Simmonds (1914), in his original description, showed that the condition was the result of a destructive lesion of the anterior pituitary. Subsequent investigators such as Reye (1921, 1926, 1928, 1931) worked out in more detail the clinical syndrome due to this pathological condition. In recent years, however, articles have been published in which undue emphasis has been placed on certain of the clinical aspects, while other more important aspects have been ignored. Numerous spurious cases based on this incorrect description have been published and, with the acceptance of these cases, the general picture of the syndrome has been further distorted. In the modern literature it is usually said that the essential characteristics of the syndrome are extreme emaciation, low basal metabolic rate, and disturbance of sex function (Escamilla and Lisser, 1938; Meyer, 1938; Meyler, 1938). It must therefore be emphasized that the one primary requirement of the syndrome is that there shall have been some gross destructive lesion in the anterior pituitary. This requirement is very frequently overlooked, and among the clinical cases reported as Simmonds's disease in the last five years, only a very small percentage have had anything to suggest an organic lesion of any sort in the pituitary. A certain number of the other cases may be due to lesions in the hypothalamic region, such as gliomata or cysts (Howard and Rhea, 1936; Kimura and Kurobane, 1937; Plummer and Jaegar, 1938), but the majority appear to be only cases of anorexia nervosa. Most of the earlier literature on these latter cases has been noted by Sheehan and Murdoch (1938a); further cases, or discussions about the differential diagnosis of anorexia nervosa from organic hypopituitarism, will be found in the papers of Sheldon (1937), van Steenis (1937), Butt and Alexandrescu (1937), Jutoran (1938), Reiss (1938), Davis and Postle (1938), Rea and Hoover (1938), Dick and Dine (1938), Stevenin and Gaube (1938), Kunstadter (1938), Comby (1938), Meyer (1938), Escamilla and Lisser (1938), Nicolle (1939), Richardson (1939), and particularly in the discussion by Ryle, Sheldon, and Spence (1939).

In the cases of anorexia nervosa, the question arises whether any of the symptoms may be due to hypopituitarism, developing as a result of

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functional disturbances of the gland, either with no gross pathological basis or with only cytological alterations. In patients of this type who have died, the pituitary has been recorded either as normal or as showing changes in the proportion of the different types of cells (Escamilla and Lissner, 1938, Case 2; Richardson, 1939, Case 3; earlier cases are listed by Sheehan and Murdoch, 1938a). Cytological alterations may obviously be of the utmost significance, but their recognition and interpretation in post-mortem material is subject to many difficulties. Leaving on one side the important question of post-mortem autolysis, there is the difficulty of deciding how far the changes are due merely to the manner of death, or whether they may have been caused by metabolic disturbances or functional alterations in the rest of the body during the last few weeks of life. For example, the effects of pregnancy or of oestrone injections on the cellular make-up of the pituitary are well known, but the effects of terminal starvation have not been so thoroughly investigated. On the other hand, the absence of demonstrable lesions in the anterior pituitary (as in many cases of diabetes and infantilism) does not exclude the possibility that some functional disturbance of this gland may be primarily responsible for these diseases. Nevertheless, despite these limitations of morbid histology, it seems advisable that a diagnosis of hypofunction of the anterior pituitary should be based primarily on a knowledge of the effects of gross pathological lesions which destroy the gland.

Complete or partial loss of the anterior pituitary in human beings is due in nearly all cases to one of the following conditions. In the first three, however, there are complicating factors, so that the symptoms are not entirely due to anterior lobe deficiency.

Surgical hypophysectomy. This is an uncommon operation which involves loss of the posterior lobe as well as of the anterior lobe, and also the danger of trauma to the hypothalamus. It does, however, give information of great value for comparison with Simmonds's disease and with the results of animal experiments.

Tumours, granulomata, &c. These lesions often produce symptoms of anterior pituitary deficiency, but complicated by various pressure effects, either in the hypothalamus or throughout the brain. In addition they often compress or destroy the posterior lobe or the pituitary stalk.

Diffuse fibrosis of the anterior lobe. This is probably a syphilitic manifestation. In most cases the anterior lobe appears to be damaged only to a moderate degree, and the possible effects of the syphilis on other organs may provide serious complicating factors.

Post-partum necrosis of the anterior lobe. This is much the most common cause of true hypopituitarism. The necrosis begins suddenly as a result of easily ascertainable factors, and is almost invariably confined to the anterior lobe. In a severe case nearly all of this lobe is lost and, for the remainder of the patient's life, there are symptoms of Simmonds's disease due to the loss. The after-effects of this lesion form the subject of the

present paper. The aetiology and pathology of the original post-partum necrosis need only be summarized here as they have been fully discussed elsewhere (Sheehan, 1937; Sheehan and Murdoch, 1938a). In the literature reviewed in those two papers, reference to the five early cases mentioned by Stander (1932) was inadvertently omitted; these cases have, however, no pathological or obstetric data.

Examples of the original ischaemic necrosis of the anterior pituitary are found relatively often *post mortem* in women who die in the puerperium, and they are present in over a quarter of such fatal cases. The necrosis may be small, large, or almost complete, but it usually spares the pars tuberalis, the part just in front of the attachment of the stalk, the region of the middle lobe, and a thin layer or small scattered islets just beneath the capsule. It is caused by severe haemorrhage or collapse of the patient at delivery, and begins at the time of these complications. In patients with such a necrosis who survive the puerperium, some further gland tissue is lost by an atrophic process around the necrotic area, and then the lesion slowly heals. In the subsequent stage, months or years later, the anterior lobe consists chiefly of a small mass of loose fibrous tissue which is formed from the stroma of the necrotic area, but in nearly all cases there also remain certain areas of gland tissue whose size depends on the extent of the original necrosis. This small scarred pituitary is the standard finding in cases of hypopituitarism which originate suddenly after a delivery, and it is quite clearly the late result of the ischaemic necrosis.

Clinical Material

The purpose of the present review is to ascertain the actual clinical picture of hypopituitarism which follows post-partum necrosis, and the extent and limitations of our present knowledge of the subject. With this object a detailed study has been made of all the cases which have appeared in the literature, and in which the patient lived for more than a year after the original lesion. Those analysed in detail here consist of two groups:

- (a) All the published cases, 32 in number, in which the clinical course was confirmed by post-mortem examination of the pituitary, and
- (b) Nineteen cases with complete amenorrhoea and sufficient clinical grounds for accepting that a post-partum necrosis had occurred, but in which pathological proof is lacking.

In addition there are three groups of clinical cases which have not been analysed here in detail, but have been taken into account in forming the general picture; most of them are fairly definite examples of post-partum necrosis, and have been discussed elsewhere.

- (a) A series of 19 cases with complete amenorrhoea and other severe symptoms, recorded by Sheehan and Murdoch (1938a).
- (b) A series of 35 less severe cases, without complete amenorrhoea, but with other typical findings recorded in that paper, and of 17 similar cases in the literature tabulated as Group B in that paper.

(c) The cases described by Simpson (1883) or in the earlier literature reviewed by him. Simmonds's disease has been well known to gynaecologists for a century or more under the name of 'superinvolution of the uterus', though they also have included under this term a variety of quite different conditions causing atrophy of the uterus, such as lesions of the ovaries or excessive lactation. Simpson, however, gave a clear account of the aetiological factors and the clinical course of several cases due to post-partum necrosis, though it was not until thirty years later that the pituitary lesion was found and its importance recognized by Simmonds (1914).

As the syndrome to be described shows certain differences from those in previous reviews of Simmonds's disease, some documentation of the facts is given here. These reviews include cases of Simmonds's disease due to post-partum necrosis, but they also include cases due to less common lesions of the gland such as true fibrosis, tumours, cysts, or granulomata, and certain of the later reviews are based to a considerable extent on cases of anorexia nervosa. The most important of these reviews and general discussions are those by Graubner (1925), Reye (1926), Calder (1932), Silver (1933), Nürnberger (1934), May and Robert (1935), Kylin (1935), Stroebe (1936), Kehrer (1937), Jumon (1937), and Herrick (1938).

The cases analysed here cannot be grouped in any satisfactory classification, for reasons to be given later, so each pathological or clinical finding is therefore considered separately. The cases are tabulated according to the duration of the illness. The serial number of each case indicates the number of years from the significant delivery to the time of death or, in patients still alive, to the time of report; the letters are to distinguish cases of similar duration. The references to the cases are as follows:

- | | |
|---|--|
| 1A Stewart (1936). | 9C Brissaud and Bauer (1907). |
| 1B Suchier (1927). | 10A Jakob (1923) Case 1. |
| 2A Sheehan (1937) Case 12. | 10B Maresch (1914 a, b). |
| 2B Thür (1928) | 10C Castleman and Hertz (1939). |
| 2C Meyler (1938) Case 11. | 11A Usadel (1932) Case 1. |
| 2D Meyler (1938) Case 1. | 11B Simmonds (1914), and (1918) Case 1. |
| 3A Heinrichs (1932). | 11C Graham and Farquharson (1931). |
| 3B Hertoghe. | 11D Rose and Weinstein (1936). |
| 3C Rowe and Lawrence. | 13A Silver (1933). |
| 3D Veil (1917) Case 1. | 13B Clauberg (1934) Case 2. |
| 3E Reye (1926) Case 3. | 14A Borchardt (1923). |
| 4A Tauber (1927). | 15A Knauer (1928). |
| 4B Hoet (1933) Case 1. | 15B Snapper, Groen, Hunter, and Witts (1937) Case 2. |
| 4C Goullioud and Poncin. | 16A Lichtwitz (1922) Case 3. |
| 5A Bratton and Field (1934). | 17A Escamilla and Lissner (1938) Case 6. |
| 5B Gallavan and Steegmann (1937) Case 1. | 18A Simmonds (1918) Case 3, and Bostroom (1918). |
| 5C Jakob (1923) Case 2, and von Grabe (1923). | 19A Bini (1937). |
| 5D Reye (1928) Case 3, and (1931) Case 3. | 19B Pribram (1922), and (1927). |
| 7A Sheehan and Murdoch (1938b) Case 1. | 19C Held (1926). |
| 7B Farquharson and Graham (1931) Case 1. | 20A Rau (1935). |
| 9A Fraenkel (1916). | 22A Weiner (1937). |
| 9B Simmonds (1918) Case 2. | 23A Priesel (1938). |
| | 24A Omelskyj (1929). |

27A Meyler (1938) Case 10.

28A Gallavan and Steegmann (1937)
Case 2.

29A Reiche (1927).

30A Richter (1929).

30B Reye (1921), and (1926) Case 1, Reye
and Schurmann (1930), Reye (1931)
Case 1, and Kaminski (1933).

44A Reiche (1930).

Most of the common facts about these patients are grouped in the table, and the meaning of the various abbreviations is explained in the relevant section of the text. The age given for each patient is the age at death or, in patients still alive, the age at the time of report.

Post-mortem Findings

The pathological changes form the basis for the clinical features of the disease, so they will be considered first.

Pituitary gland. The pituitary is always much reduced in size. In the cases in which details are given its mean weight was 0.31 gm. as compared with a normal of about 0.6 to 0.7 gm. As the recorded weight includes the posterior lobe, the scar of the old necrosis, and the remaining portions of the anterior lobe, it will be appreciated that the loss of anterior lobe tissue is very much greater than the reduction of weight of the whole gland. The anterior lobe is very small, and shows the fibrillary scar of the old necrosis abutting by a sharp margin against the few remaining areas of surviving gland tissue. These remaining areas usually occupy the sites which are normally spared by the original necrosis, they are not fibrotic, and in most cases are apparently functional. The posterior lobe is nearly always normal.

The amount of anterior lobe tissue which remains in clinically severe cases is usually less than 10 per cent. of the original lobe, and often a great deal less, though exact information on this point is difficult to obtain. The cells remaining are usually chromophobe, though some eosinophil and occasional basophil cells may be present. These two factors, the amount and the cellular constitution of the remaining part of the anterior lobe, are presumably of importance in determining the course of the disease. It is difficult to obtain information as to whether any compensatory hypertrophy occurs in the pituitary; this probably occurs if the patient becomes pregnant again, but not otherwise. The occurrence of a subsequent pregnancy suggests that a moderate amount of active pituitary tissue has been left, and there is some evidence that any compensatory hypertrophy that occurs in the pregnancy does not regress after delivery; it is thus surprising that in one case (5c) so little gland tissue was found *post mortem*. The sella turcica remains unchanged, and X-ray examination shows no abnormality. Occasionally, in rather long-standing cases (10A, 19B, 19C, 44A), there are small calcified areas in the pituitary scar, but these are too small to be recognized radiologically.

Details. The histological appearances described above were found in all cases except 13A; here the lesion was atypical, as there was a diffuse fibrosis throughout the areas of remaining gland tissue, which were unusually

| Case. | Age at death or report. | % of anterior pituitary remaining. | Thyroid atrophy. | Adrenal atrophy. | Size of viscera. | Genital atrophy. | Body hair loss. | General syndrome. | Appearance. |
|-------|-------------------------|------------------------------------|------------------|------------------|------------------|------------------|-----------------|-------------------|-------------|
| 1A | 26 | sm | — | mod | — | — | none | trans | comb |
| 1B | 21 | no death | — | — | — | mod | much | mod | hypo |
| 2A | 38 | 15 | N | sl | N | N | — | mod | N |
| 2B | 37 | 5 | sev | sev | sm | sev | much | sl | hypo |
| 2C | 33 | no death | — | — | — | — | much | mod | myx |
| 2D | 32 | died. No P.M. | — | — | — | sev | all | mod | myx |
| 3A | 36 | 20 | sev | sev | sm | N | all | sev | myx |
| 3B | 39 | no death | — | — | — | — | — | sl | comb |
| 3C | 35 | no death | — | — | — | — | all | — | ? comb |
| 3D | 38 | no death | — | — | — | mod | much | sev | myx |
| 3E | 36 | no death | — | — | — | sev | much | mod | ? comb |
| 4A | 38 | 5 | mod | sev | — | sev | much | mod | — |
| 4B | 31 | no death | — | — | — | mod | some | mod | — |
| 4C | 37 | no death | — | — | — | mod | all | late | myx |
| 5A | 41 | 8 | sev | sev | sm | mod | some | late | comb |
| 5B | 51 | 8 | sl | mod | sm | sev | all | sl | hypo |
| 5C | 41 | 2 | mod | N | — | N | all | sev | hypo |
| 5D | 35 | no death | — | — | — | mod | some | mod | ? hypo |
| 7A | 37 | 33 | N | sl | N | N | — | trans | hypo |
| 7B | 40 | no death | — | — | — | — | all | sev | comb |
| 9A | 45 | — | N | sl | sm | — | all | mod | ? prog |
| 9B | 45 | — | N | sl | sm | — | all | mod | ? prog |
| 9C | 29 | Died. No P.M. | — | — | — | mod | all | mod | hypo |
| 10A | 45 | 10 | sl | mod | sm | mod | all | sev | prog |
| 10B | 33 | 5 | mod | sev | N | sev | all | v. sev | hypo |
| 10C | 48 | 10 | sev | sev | sm | sev | — | late | myx |
| 11A | 38 | 5 | mod | sev | — | ? mod | much | mod | myx |
| 11B | 46 | 5 | N | N | sm | — | — | v. sev | prog |
| 11C | 46 | 5 | — | — | sm | — | — | v. sev | prog |
| 11D | 44 | 10 | mod | sev | N | — | much | v. sev | prog |
| 13A | 53 | (?) 20 | sl | mod | sm | mod | some | v. sev | prog |
| 13B | 37 | no death | — | — | — | mod | — | — | — |
| 14A | 41 | no death | — | — | — | sev | all | mod | myx |
| 15A | 43 | 15 | sev | N | N | — | much | none | N |
| 15B | 43 | no death | — | — | — | — | all | sl | comb |
| 16A | 41 | no death | — | — | — | sev | all | sl | hypo |
| 17A | 52 | no death | — | — | — | mod | all | v. sev | myx |
| 18A | 48 | 5 | N | sev | sm | mod | all | v. sev | comb |
| 19A | 47 | 10 | sl | sev | N | ? mod | all | mod | N |
| 19B | 50 | 10 | sev | mod | sm | sev | all | mod | prog |
| 19C | 50 | 10 | sev | sev | sm | mod | some | late | hypo |
| 20A | 56 | no death | — | — | — | — | all | late | myx |
| 22A | 50 | 5 | mod | sev | N | mod | all | v. sev | myx |
| 23A | 58 | 5 | sev | sev | — | sev | much | v. sev | myx |
| 24A | 58 | 8 | mod | sev | — | ? mod | all | sev | myx |
| 27A | 53 | no death | — | — | — | mod | all | late | myx |
| 28A | 60 | 10 | sl | mod | N | mod | some | late | myx |
| 29A | 67 | 5 | sev | sev | — | ? mod | all | late | comb |
| 30A | 62 | 5 | sev | sev | — | mod | all | late | comb |
| 30B | 58 | 0 | — | — | — | sev | all | mod | comb |
| 44A | 65 | 5 | mod | N | — | sev | all | late | myx |

| Nutri- tion. | Weight lb. | Height in. | B. P. | B. M. R. % of normal. | R. B. C. per c. mm. | Hb. %. | W. B. C. per c. mm. | Eosino- phils. | Fasting blood sugar mg. %. |
|-----------------|---------------|---------------|---------|-----------------------------|---------------------------|--------|---------------------------|-------------------|-------------------------------------|
| bad | 109 | — | 118/88 | — | 4.8 | 55 | 5.7 | 1 | 68 |
| mod | 118 | med | 85/- | -28 | 5.6 | 70 | 9.8 | 6 | 90 |
| N | — | — | 120/70 | — | an | — | — | — | — |
| N | — | — | — | — | — | — | — | — | — |
| poor | 139-103 | 63 | 100/60 | -33 | 4.4 | 94 | 5.8 | 10 | 72 |
| poor | 117-107 | tall | 90/75 | -33 | 5.7 | 68 | 5.0 | 1 | 65 |
| N | 112 | 61 | — | — | — | — | — | — | — |
| — | — | — | — | — | — | — | — | — | — |
| — | — | — | — | — | — | — | — | — | — |
| — | — | — | — | — | 3.3-5.5 | 65-70 | 4.2 | 12 | — |
| N | 147 | 65 | 100/73 | — | 4.4 | 68 | 6.6 | 5 | — |
| N | — | — | — | — | — | — | — | — | — |
| N | 121 | 61 | 115/75 | -20 | 3.8 | 66 | 6.3 | — | 97 |
| — | — | — | — | — | — | — | — | — | — |
| mod | — | — | 90/- | — | 5.3-6.3 | 86-96 | 3.0-5.6 | 1-6 | — |
| N | 120 | 67 | 140/80 | -33 | 2.7 | 63 | — | — | 68 |
| N | 112 | 62 | — | — | 4.0 | 65 | — | 11 | 70 |
| N | 190 | — | 115/72 | Near N | 4.1 | 98 | 10.0 | 4 | 140 |
| N | — | — | — | — | — | — | — | — | — |
| v. bad | 85 | 65 | 80/50 | -23 | 3.4 | 50-60 | 4.5 | — | 40-62 |
| v. bad | — | — | — | — | — | — | — | — | — |
| — | — | — | — | — | — | — | — | — | — |
| — | — | — | — | — | 3.9-4.4 | — | 9.3-17 | — | — |
| mod | 100 | — | — | — | — | 65 | — | — | — |
| poor | — | 62 | — | — | 4.0 | — | 6.1 | 2 | — |
| N | 115 | sm | 160/100 | -28 | 4.5 | 85 | 5.5 | — | — |
| poor | — | — | — | — | an | — | — | — | — |
| bad | 103 | — | — | — | — | 50 | — | — | — |
| v. bad | — | — | — | — | — | — | — | — | — |
| mod | — | — | 80/60 | -28 | 3.1 | 62 | — | 0 | 80 |
| v. bad | 60 | — | 120/80 | -10 | 2.6 | 47 | 6.4 | — | 90 |
| — | — | — | — | — | — | — | — | — | — |
| N | fat | — | 90/- | — | — | — | — | — | — |
| mod | — | — | — | — | — | — | — | — | — |
| — | ? | 64 | 110/65 | -37 | 3.2-3.6 | 50-82 | 6.4-8.9 | 4-7 | — |
| ? | 195 | 67 | — | — | — | — | — | — | — |
| N | 140-121 | 61 | 90/70 | -39 | 3.7 | 70 | 8.6 | 3-7 | 83 |
| bad | 99 | — | 110/60 | — | 3.1 | 44 | 4.0 | 2 | 62 |
| N | — | 61 | — | — | — | — | — | — | — |
| bad | — | — | — | — | 5.5 | — | — | 0 | — |
| mod | — | 61 | 135/70 | — | — | — | 6.3 | 1 | — |
| N | — | — | 110/80 | -40 | 3.7 | 70 | 5.5 | 3 | 62-78 |
| v. bad | 103 | — | 136/80 | — | 3.4 | 65 | 4.5-9.8 | 1-5 | — |
| — | — | — | — | — | an | — | — | — | — |
| N | — | — | 120/- | — | — | — | — | — | — |
| N | 130 | 61 | 135/80 | -32 | 3.2 | 60 | 5.0 | 11 | 87 |
| N | 111 | 62 | 144/86 | -36 | 3.5 | 83 | 5.0 | 10 | — |
| mod | 101 | — | 160/90 | — | 4.1-4.8 | 56-78 | 8.2-15.0 | 5-11 | 100 |
| poor | — | — | 85/- | -35 | 2.0 | 54 | 2.8 | — | — |
| N | 120 | — | 87/- | -49 | 3.9 | 65 | 8.0 | 6 | — |
| mod | 108 | — | 160/70 | — | 3.7 | 62 | 5.4 | 0-2 | 60-140 |

large. The posterior lobe was normal in all cases except 2B and 5A, and in 11A it was recorded as actually normal in the second publication. The percentage of the original anterior lobe that remained has been estimated from the pathological descriptions, which are often short, or from illustrations of single sections of the gland. The figures given in the table are thus only very rough approximations, and may in some cases be two or three times the true figures: they are of value chiefly for comparison among themselves. The parts of the gland which remained consisted mainly of chromophobe cells. In 29A and 30A there were no other cells present; in 4A, 19B, and 19C there were a few eosinophils; and in other cases there were a few eosinophils and rather less basophils (5A, 5B, 10B, 11A, 11D, 24A, 28A). In the two patients who died shortly after a delivery, the appearances were exceptional; in 2A the cells were nearly all eosinophil with a few basophils; in 7A the appearances were those of a normal gland at delivery. As has been pointed out earlier, however, there are serious difficulties in the interpretation of the cytological appearances.

Thyroid gland. The thyroid is usually small. It is often between 8 and 13 gm. in weight, as compared with a normal of about 25 gm. The size does not, however, give any clear indication of the severity of the histological involvement. Microscopically, about one-third of the glands show normal appearances or slight atrophy, about one-third show moderate atrophy, and the remaining third a very severe atrophy with extensive fibrosis. It seems probable that these atrophic changes are the result of two factors. The great reduction or almost total absence of thyrotrophic hormone (as proved in 10c) will lead to a definite atrophy, but, in addition, the thyroid itself is subject to spontaneous changes. Many women with normal pituitaries have some degree of fibrotic atrophy of the thyroid. This develops most commonly at 40 or 50 years of age, and may produce some symptoms of hypothyroidism or, occasionally, a true myxoedema. If such a patient has also had a pituitary necrosis, not only are the clinical effects superimposed, but the atrophic process appears to be accentuated. This combination accounts most satisfactorily for the cases where the patient has a pituitary necrosis at about 25 years of age, has ordinary symptoms of pituitary insufficiency until the age of 50, and then develops what appears to be myxoedema (Castleman and Hertz, 1939). If her pituitary had been normal, she would presumably have had some thyroid atrophy at the age of 50, but few or no symptoms. In addition, it is possible for a pituitary necrosis to occur in a patient who already has a thyroid atrophy and early myxoedema (Sheehan and Murdoch, 1938a, Case 1). Such a pituitary lesion would probably cause the rapid development of full myxoedema within a short time.

Details. The degree of atrophy shown in the table is based essentially on the microscopic appearances. The abbreviations used in the table have the following meanings:

- N Normal, six patients.
- sl Slight lesions, five patients. The alveoli were rather small, sometimes with low epithelium, but usually containing colloid; there was little or no fibrosis, and only a few lymphoid follicles.
- mod Moderate lesions, eight patients. The alveoli were atrophied, but usually had some colloid remaining: there was definite fibrosis and many areas of round-celled infiltration and lymphoid follicles.
- sev Severe lesions, 10 patients. The alveoli were scanty and very atrophic, with little or no remaining colloid; there was very gross fibrosis, extensive round-celled infiltration, and numerous lymphoid follicles. Among these severe cases is included one (30A) with such extreme atrophy that the thyroid was reduced to two small nodules of fibrous tissue.

Suprarenal gland. The suprarenals are usually very much below the normal weight. In cases where details are given the average weight of both glands together is 5.5 gm. as compared with a normal of about 11 gm. There is nearly always atrophy of the cortex, often so severe that the cortex is described as 'as thin as paper'. Microscopically, in these severe atrophies there is a loss of the normal layered structure of the cortex which appears to consist mainly of zona fasciculata; the zona glomerulosa and reticularis are very thin and, in places, absent. There is rarely any fibrosis of the cortex, but the capsule is usually thickened. The cortical lipid is normal in amount in most cases, the amount bearing no relation to the degree of atrophy of the cortex or to the general nutrition of the patient. The medulla is normal except in rare instances. The atrophy of the cortex appears to be a direct result of the pituitary lesion. The pathological appearances are quite unlike those of the primary atrophy which is so commonly seen in Addison's disease, where the suprarenal shows very gross scarring with small nodules of regenerating cortical cells.

Details. The degree of atrophy of the suprarenal cortex shown in the table is assessed from the macroscopic as well as the microscopic appearances. The same abbreviations for normal, and slight, moderate, or severe atrophy are used as in the section on the thyroid. Fibrosis of the cortex was slight in 5B, 11A, 19A, and 24A; severe in 11D and 19C. Cortical lipid was normal in 2A, 2B, 4A, 5A, 7A, and 10B, but was reduced in amount in 19A, 29A, and 44A, and absent in 11D. The medulla was noted as atrophic in 11D and 13A and as scarred in 2B; in the other cases it was recorded as normal or not mentioned. Care is needed in accepting reports of atrophy of the medulla without serial sections of the whole gland.

Other ductless glands. The condition of the ovaries will be dealt with later in connexion with the clinical course of the disease. The other ductless glands are nearly always normal; any changes recorded are so rare as to be probably of no significance in the disease.

Details. The pineal was rather large (0.5 to 0.65 gm.) in 19A and 19C. The parathyroids were rather small in 5A, very fatty in 10C, and surrounded

by excess of fibrous tissue in 19B. The islets of Langerhans were rather small in 4A, 19A, and 22A. In other cases these glands, when mentioned, were recorded as normal.

Brain. Detailed examination of the brain has not been made in sufficient cases to warrant any exact conclusions. There may be lesions of two kinds, degenerative changes in the fibres or nuclei of the supra-optico-hypophyseal tract, and low-grade inflammatory appearances around some of the smaller cerebral vessels.

Details. The hypothalamus was recorded as normal in 13A and 30B, and the entire brain as normal in 19C. Lesions of the hypothalamus, possibly secondary to the pituitary lesion, were however found in two cases. Case 5B had loss of nerve fibres from the posterior pituitary in the tuber cinereum, and the supra-optic nucleus had great loss of cells with gliosis and marked degenerative changes in those remaining. There were also some minor degenerative changes in the cortical cells. Case 19A had a similar atrophy and gliosis affecting the supra-optic and also the supra-chiasmatic nucleus. More diffuse microscopic lesions were found in other cases. Case 22A had numerous patches of necrosis in the medulla with glial proliferation, and extensive perivascular cuffing with lymphocytes and plasma cells. Similar but less marked changes were found in various other parts of the brain, the cord, and the meninges. Case 11A had some adventitial cell proliferation around certain of the smaller vessels. Case 10A had lesions diagnosed as encephalitis and tuberculous meningitis. Case 3A had some calcification of vessels at the base of the brain suggesting an old encephalitis, and 28A much sclerosis of small vessels. Case 5C had diffuse cellular changes in the brain, affecting particularly the cerebellum and lower olive.

Viscera. The thoracic and abdominal viscera are often abnormally small. There is no constant relationship between the degree of splanchnomicria and the loss of body fat; seven of the 14 patients with small viscera were of normal or moderate nutrition, and two of the eight patients with normal viscera were of poor or bad nutrition.

Details. The size of the viscera is noted in the table as normal (N) or small (sm). In eight of the patients with small viscera, 2B, 3A, 5B, 10A, 10C, 13A, 18A, 19C, the actual weights were recorded as within the following low ranges: heart, 115 to 200 gm.; liver, 700 to 970 gm.; kidneys together, 150 to 200 gm.

Arterial system. There is a normal post-mortem incidence of atheroma, when the age of the patients is taken into account.

Age at death.

Atheroma.

| Years. | None. | Slight. | Moderate. | Severe. |
|----------|----------------|---------|-----------|---------|
| 33 to 38 | 2A, 2B, 3A, 7A | 10B | — | — |
| 41 to 48 | 10A | 5B | 5A | — |
| 50 to 53 | 19B | 22A | 13A, 19C | — |
| 60 to 67 | — | 30A | 29A, 44A | 28A |

Bone marrow. The bone marrow is usually normal, but may show some erythroblastic reaction, possibly in relation to the anaemia.

Details. There was normal fatty marrow in 10A, 11A, 19B, and 19C. The femur showed red marrow in its upper third in 24A, and in its upper three quarters in 4A.

Intercurrent pathological conditions. As was noted by Simpson (1883), these patients have an undue susceptibility to tuberculosis, and this may possibly be related to the endocrine insufficiency. They are also unduly liable to develop rheumatism in the knees; an endocrine explanation can also be suggested here, though it is impossible to correlate the rheumatism with the degree of thyroid atrophy. There is a high incidence of urinary infections of the cystitis-pyelonephritis group, but less significance can be attached to this condition as most of the patients are multiparae. The proportion of cases in which old valvular lesions were found in the heart *post mortem* is very little higher than the proportion of cases showing such lesions in the autopsy records of any general hospital; this condition thus appears to have no special significance. Terminal broncho-pneumonia is found in a few cases, as would be expected from the type of death. It is of interest that, despite the age of the patients and the fact that most of them are multiparae, malignant disease has not been recorded except in one doubtful clinical case (Simpson, 1883, Case 11, a sarcoma of the thigh). Speculations on this subject are however premature, as the series is not large enough for negative results to be significant.

Details. There was extensive and fatal tuberculosis in 2D, 9C, and 15A, old-standing pulmonary tuberculosis in 4A, 9A, 17A, and 19A, and apical scarring in 11B. In 10A a tuberculous meningitis was recorded. Acute pyelo-cystitis was present in 2C, 28A, 29A, and 30B, old pyelonephritic scars in 5A, 22A, and 44A, and chronic cystitis in 5B. Broncho-pneumonia, which appeared to be merely terminal, was found in seven patients; early in 1A and 5B, more advanced in 10C, 11A, 18A, 19A, and 29A. An old healed endocarditis was found in 4A, 10A, 28A, and 29A. A history of rheumatism, usually affecting the knees, was given in 5B, 10A, 10C, 15A, 24A, and 28A; in some of these cases osteoarthritic changes were found in the knee-joint *post mortem*. Certain other conditions were found in individual cases: accrete placenta in 2A, acute fibrinous laryngitis in 4A, utero-placental apoplexy in 7A, hyperplastic gastritis in 13A, and atrophic gastritis in 19B. Syphilis was uncommon: 3E had a positive Wasserman and 29A a syphilitic aortitis; 16 other cases had negative Wassermans.

Other conditions. A number of other features noted *post-mortem* are discussed below in connexion with the clinical aspects of the disease. These include the state of bodily nutrition, the condition of the genital tract, and the appearance of the skin and hair.

General Clinical Aspects

In any individual case, the clinical picture, even though only partial, is nearly always typical and the diagnosis is a matter of no difficulty. The following description is based essentially on the cases with post-mortem proof of the pituitary necrosis, but consideration is also given to the purely clinical cases. A few of the patients first came under observation in terminal coma, and the clinical details of these are scanty. The various general difficulties that interfere with any satisfactory grouping of the cases may be summarized as follows:

(a) As was shown by Simmonds (1918), a fairly large amount of anterior pituitary tissue must be lost for recognizable symptoms to occur. Adopting arbitrary figures for the sake of example, there will probably be no symptoms with a loss of less than 50 per cent. of the gland, the symptoms will be slight with a 60 per cent. loss, moderate with a 75 per cent. loss, and severe with a 95 per cent. loss. The necroses which follow these complicated deliveries vary in size from 1 to about 98 or 99 per cent. of the gland, so that there is a possible range of subsequent symptoms from normal health up to evidence of almost complete absence of the anterior pituitary. In practice the lesser grades of hypopituitarism appear to be much more frequent than the severe ones, but they are rarely diagnosed or recorded and are not dealt with in detail in this paper. Nevertheless this quantitative aspect of Simmonds's disease is fundamental and should never be disregarded.

The relationship of the syndrome to the extent of the pituitary lesion holds good in a general way. Many women who have had a delivery complicated by haemorrhage or collapse remain afterwards in absolutely normal health, and at death there is a scar involving only a small amount of the anterior pituitary. If, on the other hand, there are severe subsequent symptoms, the scar is usually found to replace nearly all of the anterior pituitary, but it is not possible to establish finer degrees of the quantitative relationship. A patient who has lost 85 per cent. of the gland usually has less severe symptoms than one who has lost 95 per cent., but she may have more severe symptoms. One of the most striking examples is 5c, in which the anterior pituitary was almost completely destroyed, but the patient had two subsequent pregnancies.

It is clear that other than purely quantitative factors may play a part in the symptomatology. The situation of the remaining part of the anterior lobe may be of importance with regard to its cellular constitution, the proportion of the three types of cells differs in different parts of a normal gland, and this suggests a possible relative localization of function. Such a view would explain some of the difficulties raised in the following section, though the evidence is quite insufficient to draw any conclusions.

(b) The symptoms can involve almost any system in the body. They are of very varied incidence, and practically every one of them 'may or may not occur' without any satisfactory explanation of its presence or absence.

Furthermore, they do not show any regularity of association. For example, arranging the symptoms in the order of their apparent severity as A, B, C, and D, it might be expected that a slight case would have symptoms A++, B+, C-, D-, and a severe case A+++, B+++, C++, D+. While there is a definite tendency towards this type of association, many cases have quite irregular combinations such as A+, B+++, C-, D++.

(c) The course of the syndrome is also very variable. The general symptoms do not begin suddenly and completely when the pituitary becomes necrotic (the exceptional case 19B is discussed later). In some cases the symptoms develop gradually and progressively, in others they begin rather suddenly after a latent period which is symptomless apart from amenorrhoea and may last for many years; in many of the less severe cases the symptoms improve slowly a year or two after the delivery.

(d) It is not possible to establish any constant correlation between the clinical findings and the pathological changes in other ductless glands. Patients with gross atrophy of the thyroid usually have symptoms suggestive of myxoedema, and patients with gross atrophy of the suprarenals may have hypotension and asthenia, but there are several anomalous cases where the pathological findings will not explain the clinical course.

As a result of these difficulties, it is necessary to consider each symptom individually. They can, however, be grouped in three sections. Firstly, those symptoms developing in the puerperium of the significant delivery. Secondly, the various symptoms which characterize the ordinary course of the disease during the years after the delivery, and the possible methods of treatment. Thirdly, the terminal stage and manner of death. As far as possible, these sections are kept separate; purely terminal conditions are not discussed in connexion with the general symptomatology.

Early Clinical Features

Delivery. The disease always dates from a delivery at which the patient has been in collapse, usually as a result of severe haemorrhage. In general, the worse the patient's condition at the delivery, the severer are the subsequent symptoms. The collapse is due to some obstetrical complication, such as retained placenta, post-partum haemorrhage, placenta praevia, accidental haemorrhage, or obstetrical shock. Many of the patients first come under observation many years after the delivery, and details about it may not be obtainable. Nevertheless, the obstetric history is absolutely characteristic when it can be obtained, and it is essential for a definite diagnosis during the patient's life. If the delivery can be proved to have been normal, the patient's symptoms, however severe, cannot be ascribed to a post-partum necrosis. Conversely, if there has been severe haemorrhage or collapse at the delivery, it may be accepted that even slight symptoms of the type to be described in the next part of the paper are in all probability due to a post-partum necrosis of the anterior pituitary. Of course, every symptom

that may follow a difficult delivery is not necessarily dependent on the pituitary.

Details. Most of the evidence on this matter is summarized by Sheehan (1937), and the further evidence is given in Sheehan and Murdoch (1938*a*). Of the new cases discussed here, 2C, 2D, and 17A had much blood loss at the significant delivery, but there are no obstetrical data in 10C, 22A, 23A, and 27A. The age at which the delivery occurred may be found by subtracting the serial number (which indicates the duration of the illness) from the age of the patient at the time of death or report.

Puerperium. During the first few weeks after the delivery, the symptoms are not very striking. This is in some ways rather surprising, for the sudden destruction of nearly all of the anterior pituitary might have been expected to produce the sudden onset of some easily recognizable clinical disturbance. Any changes that may occur in the puerperium as a result of the pituitary necrosis tend to be overshadowed by the seriousness of the patient's condition from an obstetrical aspect, and their significance is thus not usually recognized. The patient has almost died at delivery, in most cases as a result of a severe haemorrhage, and an immediate return to perfect health is scarcely to be expected, even assuming that the pituitary has escaped damage, but the rarity with which symptoms are noted in the puerperium is not only a matter of their being overlooked. In recent years it has been possible to diagnose pituitary necrosis with relative certainty from the obstetrical history alone, and a number of these cases have been studied personally throughout the puerperium. The diagnosis was made on the day after delivery, and a careful watch was kept in the following days for any clinical evidence suggesting pituitary disturbance. The patients were naturally weak after the complicated delivery and blood loss, they had usually a rapid pulse for several days, and a temporary oliguria with an associated raising of the blood-urea was common. Certain of them developed complications such as pneumonia or sepsis which were sometimes fatal, and these patients were often comatose before death, but, when allowance is made for these factors, most of the patients were remarkably well during the puerperium. The only features which could be ascribed to the pituitary lesion were those discussed below, namely inhibition of lactation and low blood-sugar. It should be noted that the existence of the pituitary necrosis was confirmed in all these patients; by post-mortem examination in those who died or, in patients who survived, by the finding of typical clinical symptoms on examination a year later.

In severe cases, there is usually a complete absence of mammary activity during the puerperium; instead of the normal development of swelling and hardness at the fourth day after delivery and the establishment of lactation, the breasts shrink rapidly and remain dry. In patients whose subsequent symptoms of hypopituitarism are only moderate, this condition occurs in only about half the cases. It also occurs, however, in some patients who

have no subsequent evidence of a pituitary lesion. Its significance is uncertain; it may be due to the lack of hormones from the pituitary as a result of the necrosis, or it may possibly be only a direct effect of the complicated delivery.

During the puerperium it appears, from unpublished observations, that the blood-sugar may remain at a low level, sometimes in the region of 50 mg. per 100 c.c. It is difficult to obtain further data on this matter because in this hospital, immediately the pituitary lesion is diagnosed, the patient is treated with large quantities of glucose throughout the puerperium to prevent any hypoglycaemia which might predispose her to infection, and this treatment of course interferes with the estimations. The condition may, however, be the same as that described as hypoglycaemic shock after delivery by Levy-Solal (1932).

Details. Information about the puerperium is given in only a few of the published cases, as most of the patients with Simmonds's disease do not come under observation until a few years after the delivery. Cases 4B, 10B, and 15B had no lactation, and 24A had only slight lactation. Fuller information on this point will be found in Sheehan and Murdoch's (1938a) paper. One quite exceptional case requires comment. Case 19B developed, within four weeks after delivery, a striking progeria with wrinkled skin and loss of all her teeth. The rapid development of these symptoms suggests that they were the result of the puerperal sepsis which occurred in this case, and that they were not due to the pituitary lesion.

Clinical Condition in the Developed Disease

Menstruation and the genital tract. In the severest cases the ovaries become very atrophic and their functions are completely lost, involving disturbances of menstruation, loss of hormone control of the genital tract, and lack of follicular development. The absence of oestrogenic hormones is characterized by complete genital atrophy, namely superinvolution of the uterine body and cervix, atrophy of the endometrium to a thin layer of epithelium, loss of glycogen in the vaginal epithelium, loss of the acid reaction and Döderlein's bacilli in the vaginal secretion, and shrinkage and a senile appearance of the vagina and vulva. These organic changes are associated with a permanent absence of menstruation or molimina, dating from the delivery. There are sometimes related menopausal symptoms, such as flushing of the face, for a year or two, but these are inconstant. Less severe cases have the permanent amenorrhoea, but not the complete genital atrophy, though the uterus is usually smaller than normal. In less severe cases still, there is a return of menstruation nine to eighteen months after delivery, but it is scanty and occurs only occasionally at irregular intervals of a few months. Some of these cases improve gradually until menstruation is almost normal again, others cease menstruating after a few years. None of these patients have any true genital atrophy. Finally there is a series of minor cases with various grades of menstrual disturbance, such as an initial long amenorrhoea

followed by regular though slight menstruation, irregular scanty periods without the initial amenorrhoea, and so on up to patients with normal menstruation.

Though sterility is, of course, the rule in severe cases, subsequent pregnancy may occur in patients who have had no menstruation since the significant delivery, and has been induced in one patient who had also a complete superinvolution of the uterus and genital tract. In cases with menstruation or pregnancy after the significant delivery, the amount of anterior pituitary tissue remaining is sometimes relatively large (15 to 30 per cent. of the original gland), but there are cases where at autopsy practically no remaining tissue was found. It should be noted that the assessment of genital atrophy is only satisfactory in patients up to the age of 45 years. Many of the patients are 50 or 60 years old at the time of examination or death, and an ordinary post-menopausal involution of the genital tract cannot then be excluded as the cause of the atrophy.

Details. Among the cases with post-mortem proof of the pituitary lesion, scanty irregular menstruation occurred for three to eight years after delivery in 3 A, 30 A, and 30 B, subsequent pregnancies, from one to five in number, occurred in 2 A, 5 C, and 7 A. No information is given in 2 B, 4 A, 9 B, 10 A, 22 A, and 29 A, but all the rest had permanent amenorrhoea since the delivery. All the 19 cases without post-mortem proof of pituitary lesion had a permanent amenorrhoea, and this is the basis of their inclusion in the present series. It should be emphasized here, however, that there are many equally reliable cases of pituitary necrosis in the 52 cases without complete amenorrhoea referred to earlier.

The degree of atrophy of the ovaries, uterus, and lower genital tract is shown in the table, the abbreviations having the following meanings: N, *normal*; mod, *atrophy of ovaries and uterus*; sev, *gross atrophy of the entire genital tract*. From the published descriptions it is often very difficult to differentiate the moderate and severe groups, and some errors may be present in this division. It will be seen that the four patients with normal genitalia were those who had had menstruation or pregnancy after the original pituitary necrosis and had died before the age of 45 years. All the other patients up to the age of 45 had some degree of genital atrophy, as well as all the patients who were over that age.

Libido. Loss of libido develops in many of the patients, but is often not ascertained owing to the illness of the patient when she first comes under observation. It appears to be related to myxoedematous symptoms in some cases, but not in others. It may occur in patients who have menstruation after the delivery, as well as in those who have permanent amenorrhoea and complete genital atrophy.

Details. Libido was lost in 1 B, 3 C, 3 E, 4 B, 5 D, 11 D, 13 A, and 16 A, who had amenorrhoea since delivery, and in 3 A and 30 B, who had menstruation after delivery. It was reduced in 3 D, 18 A, and 19 C.

Body hair. In severe cases there is loss of axillary and pubic hair. This is a gradual process which may be obvious within a few months after delivery, but is rarely complete in less than five years. In less severe cases the hair is only thinned, and the loss is most marked in the axillae and least over the labia. The loss of body hair appears to be a symptom of a severe pituitary lesion. Nearly all the cases have superinvolution of the uterus and permanent amenorrhoea, though there is sometimes a loss of body hair in patients who have a normal uterus and scanty irregular menstruation. It is not possible to establish any constant relationship between this change and the degree of atrophy of the suprarenal cortex.

Details. The amount of body hair loss is shown in the table, under the progressive designations—none, some, much, or all, the last indicating a complete loss. The hair was lost rapidly in 10B, 11A, and 19B, but gradually in the other cases where information is given.

General symptoms. Most of the patients develop a group of somewhat related general symptoms which may be considered together, asthenia, apathy, and undue sensitivity to cold. While the more severe cases usually show a full development of all three symptoms together, the less severe cases may have various combinations of them; sometimes the physical disturbances are present with little or no psychological change, and sometimes the opposite condition obtains. There are also many variations in the course of development of the syndrome. Usually the symptoms develop out of the initial weakness after the delivery, and the patient seems not to recover her normal health after a reasonable period of convalescence. At this stage the symptoms are usually not very severe. In milder cases they may clear up within a year or two, but usually they continue and may become gradually worse. After several years there may be a rapid deterioration in the patient's general condition, leading to death in a few months. In other cases there is the same long period of moderate symptoms, but the terminal phase is prolonged, and during the last few years of life the patient is a permanent invalid and usually bedridden. There are also many cases where the patient is quite well during a latent period of many years and develops symptoms only in the last few years; these symptoms are usually more myxoedematous in type than in the other cases.

Brief consideration may be given to the three groups of symptoms separately. The asthenia may be of any gradation of intensity. The less severely affected patients are able to do light housework, more severe cases spend most of the day sitting quietly in a chair and may have an unsteady gait, and some patients become so weak that they are confined to bed during the later stage of their illness, from a month or two up to several years. It is difficult to assess how far the inability to work is physical and how far mental in origin, but its severity frequently does not correspond with the severity of the more obviously mental symptoms.

There are also various grades of the psychological change, which shows

some similarities to the apathy of myxoedema. It may be obvious quite early, but often it develops gradually after the asthenia. A common description is that the patient becomes dull, listless, and indifferent, neglecting the condition of her home and children. She is disinclined to talk and cannot keep up a conversation, she loses her initiative and her spontaneous interests, stays at home, and avoids company. Sometimes she becomes forgetful and makes stupid mistakes through absent-mindedness. In the severer grades the mental processes are sluggish, the speech is slow, monotonous, and slurred or unintelligible, and the face has a weary expression. There is often an associated anorexia, particularly in the more severe cases or terminally. In some cases there is a fear or distrust of medical attention, and a more complete history of the case can be obtained from the relatives than from the patient herself. Headaches are troublesome only in a few cases. Somnolence is rather common as a late symptom, usually when the rapid deterioration in the patient's general condition occurs. It is often associated with appearances suggesting myxoedema, and is probably endocrine rather than hypothalamic in origin, though cataleptic attacks have been recorded in one patient. More marked mental symptoms are rather frequent in the last few months, ranging from oddness or alternating attacks of excitement and depression up to definite insanity. Abnormal sensitivity to cold is present in many cases; the patient wears extra clothes, but cannot keep warm, and sits near the fire much of the day. This symptom is nearly always associated with a lowering of the basal metabolic rate.

Details. The course of development and the severity of the general syndrome is shown in the table. The cases are arranged in groups which are indicated as follows:

- None No symptoms (one case).
- sl Slight symptoms only (five cases).
- mod Moderate symptoms, remaining stationary or slowly progressive (16 cases).
- sev Moderate symptoms progressing slowly until the last few months, when the general condition deteriorated rapidly and the patient was severely ill (six cases).
- v. sev Similar moderate symptoms, progressing slowly to a long final stage of one to eight years, when the patient was a permanent invalid and usually bedridden (nine cases).
- late Cases where the patient had no general symptoms, during a long latent period, sometimes twenty years or more, but then developed symptoms for the last one to five years. These symptoms were usually more typically myxoedematous than in the other groups, and the condition has been discussed earlier in connexion with the pathological findings in the thyroid (10 cases).
- trans Cases where the patient had definite symptoms during the first few months, but improved subsequently (two cases).

Mental changes of various degrees of severity and often only as a pre-

terminal phase were noted in 4A, 5C, 7B, 10A, 10C, 17A, 18A, 19A, 22A, 28A, 30A, and 44A; cataleptic attacks occurred in 19B.

Facial appearance, skin, and head hair. The general appearances of the patients fall into five categories. The classification is based on certain general characteristics, though all the patients in a group do not show the complete picture.

The first group is that of progeria. There is an appearance of premature senility, the patient looks 10 or 15 years more than her real age, the skin is wrinkled, thin, and inelastic, and usually rather dry, and its colour is pale or slightly yellowish. The head hair is of normal amount or quite thick, and is sometimes of its original colour, but sometimes has gone grey; the eyebrows are normal or a little thin. These appearances are most commonly seen in patients dying at nine to fourteen years after delivery, and are usually associated with a prolonged terminal stage of invalidism with loss of weight and severe general symptoms.

The second group is a combined type, intermediate between the progeria and myxoedema groups. It is only in rare cases that the patient has any appearance of premature senility. The skin is dry, shining, and atrophic, but not usually wrinkled; it is pale or rather yellow. The head hair is short, thin, and dry, the eyebrows are very thin or lost. This condition may be seen in any stage of the illness.

The third group is the most common one, and it consists of patients with general appearances suggesting myxoedema. The skin is dry and scaly, there is often some diffuse subcutaneous thickening. The head hair is thin, dry, and sometimes coarse, and the eyebrows are lost, or at any rate very thin. This condition may develop quite rapidly in the first two or three years after delivery, but is more frequently only one aspect of the late development of symptoms in patients who have been well until twenty or thirty years after delivery. Some of the cases have severe atrophy of the thyroid *post mortem*, but this is not invariable.

The fourth group is made up of certain hypothyroid appearances insufficient to be classed as myxoedema. The patients have thin eyebrows, dry and sometimes scaly skin, and a tendency to subcutaneous oedema, but the head hair is usually normal.

The fifth group contains the patients whose appearance is either normal, or at any rate not sufficiently abnormal to attract attention. These patients are usually in relatively good health.

In view of the condition of the suprarenals it is of interest that skin pigmentation of Addison's disease type is practically never seen. The pallor or waxy colour so commonly noted in these patients may be due to the fact that many of them have been living indoors, or sometimes confined to bed, for a considerable time before they come under observation. The possibility that the pallor may be due to endocrine disturbance is, however, suggested by the contrasting condition, the purple face of the Cushing syndrome.

Loss of some or all of the teeth, either by caries or loosening since delivery, is observed in about half the cases. It is, however, very difficult to assess the significance of this symptom, as many of the patients are of fairly advanced years and would probably have lost many teeth in the ordinary course of life.

Details. The cases are classified in the table according to the above description; the abbreviations used are as follows: prog, *progeria*, eight cases; comb, *the group intermediate between progeria and myxoedema*, 11 cases; myx, *myxoedema*, 16 cases; hypo, *lesser hypothyroid appearances*, 10 cases; N, *normal*, three cases. Some skin pigmentation was noted in 2d and slight pigmentation in 19c, but, in neither case, did this in any way approach true Addisonian pigmentation.

Change in weight. In most reviews of Simmonds's disease, it is said that the fundamental symptom is emaciation, but this is quite erroneous. Actually, in the reports of patients who have died and in whom the pituitary lesion was found at autopsy, most are of above normal, of normal, or of moderate nutrition; only about one-third are described as poorly nourished, badly nourished, or very emaciated. Though many of these patients who died had had a rather rapid loss of weight during the last few months of life, only one of the recorded weights was under 99 lb. Patients who are still alive at the time of report are usually of normal weight, and often above normal.

Any loss of weight that may occur has usually a satisfactory explanation in a reduced intake of food, and there is little or no evidence that the pituitary lesion is directly responsible. There may be an original severe loss of weight as a result of prolonged puerperal sepsis. Later, some of the patients develop anorexia as part of the psychical symptoms, and in certain cases there is much vomiting. If the resultant inanition is severe and continues for a few weeks the patients usually die. In many of these cases, however, the anorexia is a temporary but recurring condition, and the patient's weight may swing 20 or 30 lb. up and down for a period of many years without serious consequences. A considerable number of the patients eat normally and remain at their usual weight. In a few cases the patient gains 20 or 30 lb. after delivery. Such a gain also occurs not uncommonly in patients after a normal delivery without any pituitary necrosis, and its cause is as yet unknown. Its chief significance is that, if it happens to occur in a patient who has had a pituitary necrosis, there is often, though not invariably, a complete absence of the general symptoms; the patient is psychically normal, is able to do her housework, and does not feel abnormally sensitive to cold.

Details. The information available on this matter requires rather more detailed review than in the other sections.

(a) Patients with post-mortem records may be considered first, as not infrequently they have some weight loss in the last few weeks of life. The

state of nutrition at death is shown in the table, and has been judged from the recorded appearance of the body or the measured thickness of subcutaneous fat. The meaning of the abbreviations used are as follows:

- N good or normal nutrition (12 cases).
- mod moderate nutrition (seven cases).
- poor poor nutrition (three cases).
- bad definitely thin (four cases).
- v. bad extreme emaciation (four cases).

In rather over half of the patients, there was a history of loss of weight at some stage of the disease. The cases in which information about the manner of the weight loss is given, may be classified as follows:

A severe weight loss in the first few months after delivery was noted in four patients. Of these, 5C, 11B, and 19B had pyrexia for several weeks after delivery as a result of puerperal sepsis or pyelitis, 1A had blindness, great mental depression, and severe anorexia with vomiting for the first five months of the puerperium. The weight was regained in 5C, but not in the others.

A gradual weight loss for some time after the delivery was recorded in seven patients, unexplained in 2B and 7A, but caused by prolonged anorexia or vomiting in 5B, 10A, 11D, 24A, and 30B. It is noted in four of these cases that the weight was regained when the food intake returned to normal. No details of the subsequent course are given in the other three, but all of the patients in this group were normally well nourished at death.

Four patients appear to have had no loss of weight until the later stages of the illness, when they developed anorexia (cases 3A, 28A, 30A, 44A). One of these was poorly nourished at death, the others were of moderate or normal nutrition.

Four patients had a gradual loss of weight after delivery, with a more rapid loss in the late stages of the illness. The weight loss was sufficiently explained by anorexia in 5A, 18A, and 22A; the last two of these patients were very thin at death. In 13A the weight loss was not accounted for; this patient was extremely emaciated at death (only 60 lb.), but the appearances of the pituitary were anomalous. One of the clinical cases (2B) may be considered also in this group, as she died emaciated as a result of severe tuberculosis, but there was no post-mortem examination.

(b) The patients who had not died were in general normally nourished, and the details of weight, height, and nutrition are shown in the table. It will be seen that 7 cases were recorded as fat or of normal nutrition, 1 of moderate, 1 of poor, and 1 of very bad nutrition. The details of the last two cases are of interest, 2C was rather fat when she came into hospital two years after delivery, but lost 36 lb. there as a result of pyelitis and anorexia; 7B had prolonged puerperal sepsis, but the weight loss continued gradually afterwards until she was extremely emaciated. This association between prolonged puerperal sepsis and a permanent subsequent loss of weight has been noted above in the section on patients who died. Among the other patients,

there was a gain of weight after delivery in 3 E, 5 D, and 14 A, and a temporary loss of weight with subsequent recovery in 17 A and 20 A. Case 16 A had ascites and oedema, so her weight is not a reliable index of her state of nutrition. It may be noted here that there was a severe loss of weight in only one of the 54 clinical cases recorded by Sheehan and Murdoch (1938 a); this patient had persistent diarrhoea and frequent vomiting since the delivery.

In both groups together, the patients who died and those still alive, there are 24 recorded weights and 15 recorded heights. Calculating from the lowest weight recorded for each patient, the mean weight is 116 lb., and the mean height is 63 in. The 'normal' weight given in the standard tables for a woman of 63 in. is 120 lb. Making all allowance for the possible fallacies of these calculations, it is impossible to interpret the figures as indicating severe emaciation.

Pulse, temperature, and blood-pressure. The pulse and temperature are usually normal. In a few cases the temperature is 96° to 97° F. or even lower, and the pulse rate only 60 to 70; this is seen more commonly in myxoedematous patients. The blood-pressure is sometimes rather low, but is more often within normal limits and may be slightly raised, particularly in the older patients.

Details. The blood-pressures are shown in the table, and in cases with several readings, only the highest is recorded. The systolic pressures may be summarized as follows:

| | |
|--------------------|----------|
| 80 to 99 mm. of Hg | 9 cases. |
| 100 to 119 " " | 8 " |
| 120 to 139 " " | 6 " |
| 140 to 160 " " | 5 " |

Electrocardiography. In the few cases in which electrocardiograms have been made, the main changes are the low voltages, and there may also be findings suggestive of myxoedema.

Details. Case 5 B had an inverted T-wave in leads II and III. Case 7 B had low voltages on all occasions. Case 10 C had tracings consistent with myxoedema. Case 17 A had small complexes in all leads and evidence of a latent partial auriculo-ventricular block, the findings suggesting myxoedema. Case 27 A had low T-waves, and 28 A had a laevo-cardiogram with slurring in leads II and III and a diphasic contour in lead III.

Gastric secretion. Judging from the few recorded investigations of the gastric secretion, half of the cases have a normal secretion of hydrochloric acid, and the others have either a slight secretion or none at all. Further work on this matter is needed. So far as it is possible to trace any relationship between the blood picture and the gastric secretion, patients with achlorhydria have usually a low colour index, and the patients with hyperchromic anaemia have usually free hydrochloric acid in the gastric juice.

Details. The secretion of hydrochloric acid was normal in 4 B, 5 B, 10 C,

11 D, 27 A, 28 A, and 29 A. The free acid was very low in 15 B and 17 A, and absent in 2 D, 5 A, 10 A, and 13 A. Achylia gastrica was noted only in 2 D and 10 A.

Basal metabolic rate. The basal metabolic rate was lowered in all cases in which measurements were made. It lies usually between -25 and -33 per cent. in patients during the first 15 years after onset of the pituitary necrosis, and appears to fall to this level quite early after the delivery, certainly within the first year. It is usually lower, -30 to -40 per cent., in the long-standing cases 20 or 30 years after delivery. It is not possible to correlate the fall in the basal metabolic rate with the degree of atrophy found in the thyroid histologically, but the number of cases in which measurements have been made is too small for satisfactory comparison. The low figures in the long-standing cases, at a stage when the thyroid is usually very atrophied, do however suggest analogies from animal experimentation; the low basal metabolic rate of the hypophysectomized animal is further reduced by thyroidectomy.

Details. The basal metabolic rates are shown in the table; figures which were raised as a result of treatment are not included.

Blood picture. Erythrocytes. There is nearly always a moderate anaemia. The general outline of its course is as follows, though there are the usual variations from case to case. During the first five years, the red-cell count is often as high as 5 to 6 millions per c.mm., with a rather low colour index of 0.6 to 0.8. In the next ten years the red-cell count usually falls to 3 to 4 millions per c.mm., but the colour index is rather higher, about 0.7 to 0.9. In the long-standing cases this condition may remain, or there may be a further fall in the red-cell count to 2 to 3.5 millions per c.mm. with a higher colour index, from 0.95 to 1.25. These hyperchromic anaemias are more often seen in cases in which there is a severe hypothyroid element.

Leucocytes. The number of leucocytes is normal or a little low, usually between 4,000 and 6,500 per c.mm. A relative, but not an absolute, lymphocytosis is often present; in the 16 cases in which a differential count was published, the average figures were 2,300 lymphocytes and monocytes, and 3,400 polymorphonuclears per c.mm. An eosinophil leucocytosis is common. In about one-third of the cases the eosinophil count is below 2 per cent., in about one-third it is from 3 to 6 per cent., and in the others it is from 7 to 12 per cent.

Details. The table shows the erythrocyte count in millions per c.mm., the percentage of haemoglobin, the leucocyte count in thousands per c.mm., and the percentage of eosinophils in the differential white count.

Blood chemistry. The non-protein nitrogen and urea in the blood are usually normal or in the upper part of the normal range. Cholesterol is also sometimes above normal, frequently at about 280 to 320 mg. per 100 c.c., and this may be related to the hypothyroidism. The fasting blood-sugar is often low having regard to the methods of estimation which have

been employed, being in about half the cases between 60 and 70 mg. per 100 c.c., and in the remainder between 80 to 100 mg. per 100 c.c. or higher. Sugar tolerance tests give curves of about the normal height, but usually much prolonged, and the blood-sugar has in most cases not returned to its fasting level within two hours, and often not within three hours. There is no evidence as to which part of the glycogen storage mechanism is at fault. Insulin tolerance tests have not been made in sufficient cases to allow of any deductions.

Details. The following data are recorded in mg. per 100 c.c. of blood :

| Urea : | Non-protein nitrogen : | Cholesterol : |
|-------------|------------------------|----------------|
| 1A 38 to 61 | 7B 85 to normal | 2C 277 |
| 4B 30 | 10C 18 | 10C 374 |
| 5A 44 | 22A 36 | 11D 283 |
| 13A 30 | 29A 26 | 17A 118 to 212 |
| | 44A 18 | 27A 322 |
| | | 29A 292 |
| | | 44A 560 to 96 |

Various other substances in the blood have been estimated without any gross abnormalities being found (Cases 5B, 10C, 11D, 22A, 28A, 29A, and 44A). The fasting blood-sugars are shown in the table, and it should be noted that these do not include any terminal figures. Calculating from the lowest figure in each case, the mean is 78 mg. per 100 c.c.

The recorded sugar tolerance tests give the following figures (mg. per 100 c.c.):

| Case. | Fasting level. | $\frac{1}{2}$ hr. | 1 hr. | 1½ hrs. | 2 hrs. | 2½ hrs. | 3 hrs. |
|-------|----------------|-------------------|-------|---------|--------|---------|--------|
| 1A | 68 | 120 | 100 | 100 | — | 68 | — |
| 2D | 65 | 91 | 142 | 179 | 160 | 94 | 83 |
| 4B | 97 | 163 | 160 | 111 | 90 | 102 | 98 |
| 5B | 68 | 116 | 120 | — | 105 | — | — |
| 7B | 62 | — | 120 | — | — | — | 62 |
| 17A | 83 | 110 | 125 | — | 114 | — | 92 |
| 20A | 64 | 136 | 80 | 70 | 96 | 90 | 80 |
| 27A | 87 | 87 | 108 | 147 | 143 | 152 | 134 |
| 44A | 120 | 160 | 210 | 130 | 110 | 110 | 100 |
| Mean | 79 | 123 | 129 | 120 | 112 | 99 | 87 |

The mean figures given above are calculated from the recorded figures, with interpolations where necessary. The general significance of these means can be assessed by examination of the actual data.

Insulin tolerance tests appear to have been made on only two of the patients. Case 4B was given 5 units of insulin, and her blood-sugar fell gradually from 101 down to 89 mg. per 100 c.c. four hours later. Case 20A was given 10 units of insulin, and her blood-sugar fell from 70 down to 40 mg. per 100 c.c. in about one and a quarter hours, and then stayed at the low level for many hours afterwards.

Effects of treatment. The most reasonable treatment on *a priori* grounds is replacement therapy by the administration of anterior pituitary extracts. In a few cases this has been reported to improve the general condition of the patient, even to the extent of causing regrowth of pubic and axillary

hair, but menstruation has not been re-established. Some of the patients received treatment by injection and others by mouth, but the activity of many of the preparations used is in doubt. A number of cases have been treated without any obvious improvement, and the results in general are not very satisfactory.

Thyroid extract usually raises the basal metabolic rate, sometimes nearly to normal, and improves certain of the cases with a gross myxoedematous element, but sometimes it produces vomiting which may be related to the adrenal insufficiency, as suggested by Castleman and Hertz (1939). It causes loss of weight in some patients and gain in weight in others, possibly by improving the apathy and the associated anorexia. Many patients, however, show little or no response to thyroid medication.

Suprarenal cortical hormone produced some benefit in one case. Extracts of pregnancy urine are invariably useless. Oestrogenic hormones cause a temporary hypertrophy of the uterus followed by a withdrawal bleeding, but do not have any lasting effect. The anaemia is sometimes improved by large amounts of iron.

The most hopeful line of treatment is physiological. If the patient becomes pregnant, either spontaneously or as a result of treatment directed to this end, there is usually a very marked improvement in her general condition during the pregnancy. After the delivery, normal menstruation usually begins again and the patient remains free from any evidence of hypopituitarism subsequently. This complete symptomatic cure can be obtained even in severe cases, and is probably the result of a hypertrophy of the remainder of the pituitary tissue, which occurs under the influence of pregnancy and does not regress after delivery. This subject is dealt with in more detail by Sheehan and Murdoch (1938 *b*, 1939).

Details.

Anterior pituitary extracts:

- Definite improvement, 1B, 3E, 4B, 5D, 30B.
- Slight improvement, 3C, 17A, 20A, 27A.
- No effect, 2C, 18A, 29A, 30A.

Thyroid:

- Definite improvement, 3D, 11A.
- Slight improvement, 2C, 2D, 5B, 11D, 14A, 15B, 17A, 22A, 27A.
- No effect or made worse, 5A, 7B, 10B, 10C, 20A, 28A.

Suprarenal cortex:

- Slight improvement, 27A.

Pregnancy urine extracts:

- No effect, 2C, 5B, 13B.

Oestrogenic hormones:

- Withdrawal haemorrhage, 13B.

Iron:

- Anaemia improved, 1A, 5A.
- No effect, 7B, 15B.

Final Clinical Stages

Terminal phase and manner of death. A few patients die of other conditions, such as subsequent obstetrical complications or tuberculosis, but the great majority die in coma. This coma is sometimes preceded by a short phase of mental confusion or delirium, and is usually fatal within about one day. Sometimes it is accompanied by convulsions or by muscular rigidity of jaws or limbs. In some cases the pulse-rate and temperature are very low (40 to 50 per minute and 94° to 95° F. respectively), but, rather more frequently, there is a pyrexia of 101° to 105° F. and a rapid pulse. This pyrexia may be associated with leucocytosis and a rising blood-urea, but is not usually related to terminal broncho-pneumonia.

Some of these comatose patients have a severe hypoglycaemia, and intravenous glucose can sometimes produce a cure of the coma. The evidence on these matters is very scanty, but it seems probable that further studies will show that the coma is often hypoglycaemic. The blood-sugar values that have been recorded several weeks or more before death were not very low, and it appears that any extreme hypoglycaemia develops as a relatively sudden attack. In certain cases there are minor clinical features suggesting that less severe hypoglycaemic attacks had occurred at intervals for a few days or weeks before death: some patients, e.g. 44A, have certainly a very variable fasting blood-sugar at that time. The theory that the coma is frequently of hypoglycaemic type is supported by the history of the preterminal stage. Whenever details about this are given, the coma was preceded by a short period of grossly insufficient food intake; this was sometimes due to an intercurrent illness, and sometimes to severe anorexia or vomiting.

Some of the cases of coma not associated with hypoglycaemia may be due to Wernicke's encephalopathy following malnutrition, and comparable to the cerebral lesions of hyperemesis or carcinoma of the stomach. Some of the patients have vomiting or anorexia for several weeks before death, and there may be signs suggesting an avitaminosis (10C, 11D, 18A, 22A). At this stage, a number of the patients have various mental disturbances which may be of definite Korsakoff type. Specific examination of the brain for Wernicke lesions has, however, not been made in sufficient cases to justify any conclusions.

Details. Cases 2D, 9C, and 15A died of tuberculosis, 2A and 7A of obstetrical complications in subsequent deliveries. No exact details about the manner of death are given in 5C, 9B, 23A, 29A, and 30B, and only the fact that death was sudden is noted in 13A and 44A.

All the remaining 21 patients died in coma. During the coma there was muscular rigidity in 1A, 3A, 10A, and 24A, and fits in 2B, 5A, 5B, and 10B. The temperature was very low in 5B, 5C, 10A, and 19B, but high in 3A, 10C, 11B, 11D, 22A, and 28A. Among these pyrexial cases the leucocyte count was 25,000 per c.mm. in 11D and 14,000 per c.mm. in 28A; there was broncho-pneumonia in 10C and 11B. The blood-urea was normal in

5B, but slightly raised (to about 50 mg. per 100 c.c.) in 3A and 28A; in 11D it climbed steadily to 202 mg. per 100 c.c. at death. The systolic blood-pressure was 120 to 140 in 5B, 19C, and 24A, but only 90 or less in 19B and 28A.

The blood-sugar was estimated in five of the comatose patients. In 28A and 44A it was 60 to 74 mg. per 100 c.c., but in 5B, 11D, and 19C it was only 15 to 34 mg. per 100 c.c. The coma was cured temporarily by intravenous glucose in two of these patients, 11D and 44A, and also in two other patients without recorded blood-sugar estimations, 5A and 19B. Three of these patients died a few days later with recurrence of the coma, and the other, 11D, with a rapidly rising blood-urea, as noted above. Treatment with intravenous glucose was of no avail in one of the other hypoglycaemic patients, 5B, but she had already developed broncho-pneumonia.

The insufficient food intake which immediately preceded the coma and death was due to fibrinous laryngitis in 4A, diarrhoea in 10B and 13A, food-poisoning in 11A, alveolar abscess in 19A, cystopyelitis in 28A, 29A, and 30B, and vomiting or severe anorexia in 3A, 5A, 10A, 10C, 11D, 19C, 22A, and 44A.

The clinical history and pathology of the brain in 22A was suggestive of subacute Wernicke's encephalopathy, and some of the cerebral lesions in other cases noted in the section on brain may possibly have been of this type also.

Discussion

This type of Simmonds's disease is much the most common; other true types, such as those due to tumours, granulomata or fibrosis, are rare and liable to have complications besides the pituitary insufficiency, as has been indicated above. In certain respects the actual syndrome differs from that given in the standard descriptions, and the chief points are considered below:

(1) Various authors have noted that the onset of Simmonds's disease can very frequently be traced to a delivery. This has given rise to many speculations as to the nature of the change that occurs in the pituitary. When the entire pathology of the condition is unknown, the view is put forward that the involution of the hypertrophied pituitary which occurs normally after delivery is excessive in these cases. When the late scarred stage of the pituitary is known, but the original lesion is not known, a theory of essential atrophy of the gland is sometimes offered. When both the early and late stages of the lesion are known, the condition is ascribed either to embolism or thrombosis. There is, however, practically never any possible source for emboli. A detailed study of the thrombi in the pituitary vessels in these cases is at present in progress.

The obstetrical aspects have also received some attention. Simpson in 1883 noted the relationship of the clinical disease to severe haemorrhage at

delivery, but his work has received little attention. Complications at the delivery are sometimes referred to, but more significance is usually placed on a history of puerperal sepsis. It must therefore be emphasized that, though puerperal sepsis is common in patients who have had severe haemorrhage at delivery, it begins a day or two after the pituitary necrosis has occurred. Attempts have also been made to explain the lesion as due to toxæmia of pregnancy, analogous to the liver lesions of eclampsia; actually the significance of the toxæmias is that they may predispose to collapse at delivery. Multiparity and a rapid succession of pregnancies have both been held to blame as in some way leading to 'exhaustion' of the pituitary; the actual significance of these factors is that they render a woman more liable to have retained placenta, placenta prævia, or accidental haemorrhage.

In contrast to the variety and vagueness of these explanations, the true aetiology of the original lesion is quite simple. Every woman who nearly dies of haemorrhage or collapse at delivery develops a large pituitary necrosis, and it can be accepted that any patient who does die from these causes at delivery would have developed a pituitary necrosis if she had lived long enough. Patients who are seriously ill from these causes at delivery usually have necroses, and these necroses are usually large. Patients who are only moderately ill have necroses less commonly, and the lesions are usually small. The subsequent fate of the patient depends essentially on the size of the lesion. Thus it will be seen that a reasonable clinical diagnosis of the pituitary necrosis can be made within an hour or two after delivery, that is, at a time when the lesion is too early for histological recognition. At this time also, it is possible to give a fairly accurate prognosis as to the chances that the patient will develop Simmonds's disease in the years to come. Taking the sequence in the reverse way, when a patient has clinical symptoms which suggest Simmonds's disease, the diagnosis can be made by looking back through the records of the obstetric hospital in which the patient had her deliveries. Further, if cases are required for study, they can easily be obtained by going through the previous records of an obstetric hospital and following up those patients who nearly died at delivery as a result of haemorrhage or collapse.

(2) It is sometimes considered that Simmonds's disease is a sharply defined entity due to complete loss of pituitary function. From the cases analysed, it will be seen that the anterior pituitary is never completely lost, and even in severe cases there is nearly always some recognizable trace of the gland left. In addition, many cases occur where the symptoms are of only moderate severity and the pituitary shows considerable damage, and many other cases where the woman is free from symptoms, but the pituitary shows slight to moderate lesions. These latter cannot, of course, be accepted clinically as cases of Simmonds's disease, but, from a theoretical aspect, they may be considered as sub-clinical cases. They differ quantitatively, but not qualitatively, from the severe cases in which a diagnosis of Simmonds's disease is justified. In a patient who has had a post-partum necrosis, the

pituitary insufficiency is essentially a relative matter, comparable to the question of cardiac or renal insufficiency after damage to those organs.

(3) In most reports it is stated that the characteristic and fundamental symptom of Simmonds's disease is severe emaciation. This view probably derives from the fact that three of the original cases described by Simmonds were so thin as to lead him to introduce the somewhat misleading term 'pituitary cachexia'. Silver (1933), who wrote one of the first reviews of Simmonds's disease, was probably influenced to some extent by the fact that his own case was extremely emaciated. Actually, however, as has been shown above, a severe degree of emaciation is quite uncommon, and any patient who begins to lose weight rapidly usually dies before she becomes seriously emaciated. Silver's case was, as will be seen from the table, the outstanding exception to this generalization. This standard requirement of a severe loss of weight for the diagnosis of the disease appears to be the reason for most of the errors in the diagnosis. Many true cases of Simmonds's disease are probably missed because the patients are of normal nutrition. On the other hand, a large number of spurious cases are diagnosed on the basis of a severe loss of weight, usually combined with amenorrhoea and a low basal metabolic rate; as has been pointed out by various authors (Ryle, Sheldon, and Spence, 1939), most of these are really cases of anorexia nervosa.

In medical text-books the section dealing with Simmonds's disease is usually illustrated by a photograph of a woman who is emaciated to 'skin and bone'. The visual emphasis of such photographs is unfortunately enhanced by the fact that they appear within a page or two of excellent illustrations of myxoedema and acromegaly. It should therefore be noted that these photographs of emaciated women are never taken from cases of true Simmonds's disease. Similar photographs appear in most reports of cases of anorexia nervosa that are published under the title of Simmonds's disease. By contrast, in true cases of Simmonds's disease the state of nutrition is hardly ever sufficiently abnormal to merit photographic illustration.

(4) It is also not possible to accept the standard opinion that Simmonds's disease is extremely rare. From calculations given in an earlier paper (Sheehan, 1938) it seems probable that in each 10,000 of the population there are about two severe cases and seven lesser cases of hypopituitarism due to post-partum necrosis. These figures are only approximations, but they give some idea of the true incidence. The cases come into the care of most branches of medicine, and are sometimes recognized, but more often pass undiagnosed. The general practitioner sees many of them, and may class the milder cases as prolonged debility following a difficult delivery. Severer cases with permanent amenorrhoea and superinvolution of the uterus find their way to the gynaecological out-patient departments; they used to be sent away as incurable after their first visit, though, since the advent of oestrone therapy, they are now more frequently treated. More

marked general symptoms bring the patients to the medical wards as myxoedema or anaemia, but treatment for these conditions does not produce the anticipated results. Some of the longer-standing cases come under the care of neurologists on account of mental changes. A number of them are admitted to hospitals as urgencies suffering from terminal coma. If the hypoglycaemia is recognized, the surgeon may perform laparotomy in the search for a pancreatic islet adenoma; these patients do not stand operation well, as any post-anaesthetic vomiting may precipitate coma. Finally, the cases may return to the obstetrician, who not only deals with the aetiology and thus the prevention of the original lesion, but has also what appears to be the most satisfactory treatment of the established disease.

Summary

1. Most cases of true Simmonds's disease are the late effect of post-partum necrosis of the anterior pituitary. A review is given of these effects, clinical and pathological, based on a detailed analysis of 51 published cases, and supplemented by information from over 70 other cases in the literature.

2. The original necrosis occurs at a delivery which is invariably complicated by collapse, usually as a result of severe haemorrhage. Following this there develop a number of signs and symptoms which vary in frequency and severity according to the size of the original necrosis, and probably according to other factors. The following is a condensed and composite description of a severe case, but exceptions to most of the conditions are found in individual cases:

During the puerperium there is complete absence of lactation and sometimes hypoglycaemia. After this, the uterus becomes superinvolved and the external genitalia atrophic. Menstruation does not return, and libido is absent. There is a gradual loss of the axillary and pubic hair. The patient is apathetic and dull, unable to do her housework, and very sensitive to cold. She may show a myxoedematous or a prematurely senile appearance. The weight is usually little altered unless there is great anorexia. The blood-pressure tends to be rather low, and the basal metabolic rate is about - 25 per cent. of the normal. A hypochromic anaemia is present, sometimes associated with a definite eosinophil leucocytosis. The blood-cholesterol may be a little raised, and the blood-sugar rather low, but sugar tolerance tests give a curve with a delayed fall. After 10, 20, or 30 years the patient may become more typically myxoedematous, or may develop mental changes with anorexia and some loss of weight. At this stage the anaemia may become hyperchromic, the basal metabolic rate may fall to about - 35 per cent., but the blood-pressure is usually normal. Finally, usually as a result of some intercurrent illness or a phase of severe anorexia, the patient goes into coma and dies, usually with hypoglycaemia. *Post mortem*, the anterior pituitary is represented chiefly by the large scar of the original post-partum necrosis, the suprarenal cortex is atrophic, the thyroid

usually shows fibrous atrophy, the ovaries and uterus are shrunken, and the viscera are small.

3. Substitution therapy is as yet not very satisfactory, but, if a subsequent pregnancy occurs, the symptoms are permanently cured, probably as a result of hypertrophy of the remaining portions of anterior lobe tissue.

4. This type of Simmonds's disease is relatively common, but the cases frequently remain undiagnosed. On the other hand, there are very many cases reported in the literature as Simmonds's disease which are not true examples of that condition at all. The confusion appears to arise from the misconception that patients with Simmonds's disease usually show cachexia.

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Addendum

An additional case with typical post-mortem findings is recorded by Meerwein (1938). Like several of those analysed in the present paper, it was published under the designation of Falta's multiple endocrine sclerosis. The woman was aged 60 years, and had had amenorrhoea since her second delivery at the age of 35.

EXPERIMENTAL LEUCOCYTOSIS IN MAN¹

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Introduction

SINCE the end of the nineteenth century the production of experimental leucocytosis has been the subject of intensive study, particularly in animals and, to a lesser extent, in man. Nucleic acid and its derivatives have come to be considered as the probable agents of stimulation of the bone-marrow and of the production of leucocytosis, and this conception has been supported by Jackson's (1924) isolation of nucleotide in the circulating blood. Nucleotide has been looked upon as the factor necessary for the maturation of the granular leucocytes, analogous with the anti-anaemic factor essential for complete development of the erythrocytes in pernicious anaemia.

In animal and human experiments it has been shown that injection of nucleic acid and its derivatives often produce a marked leucocytosis, but the mechanism of this is disputed. Many authors (Albert, 1937; Ames and Huntley, 1897; Antoneich, 1926; Brockmann, 1937; Doan, 1926; Doan, Zervas, Warren, and Ames, 1928; Faludi, 1938; Gotmakher-Redelman, 1926; Habetin, 1923; Hoff, 1935, 1937; Jacobi, 1920; Kracke and Garver, 1937; Laguna, 1936; Larsell, Jones, Nokes, and Phillips, 1927; Medwin, 1924; Milroy and Malcolm, 1899; Müller, 1922, 1923; Neymann, 1917; de Paolo and Calisti, 1912; Parlavecchio, Reznikoff, 1929, 1931; Sabin, 1922, 1928; Sabin and Doan, 1927; Schilling, 1925; Wallbach, 1932, 1937; and others) hold that nucleic acid is a true stimulant of the bone-marrow; others doubt whether the action is more than an alteration in distribution of the white cells in the blood-stream (Bruce, 1894; Büngeler, 1926; Goldscheider and Jacob, 1894; Gräff, 1921; Herrenknecht, 1924; Moshagen, 1934; Schulz, 1892; Weijlens, 1938; and others). In favour of the first view the investigations of Doan and his colleagues are outstanding in importance. Doan and his collaborators carried out an elaborate parallel study in animals of the blood and bone-marrow after injection of nucleic acid and various derivatives. During the first hour a leucopenia occurred in the blood with an increase of leucocytes in the spleen; thereafter leucocytosis rapidly developed, the cells being neutrophil polymorphs of full maturity and without any so-called 'shift to the left'. In the bone-marrow maturation of the myelocytes was increased in rapidity for delivery to the blood.

¹ Received March 18, 1939.

With frequent injections over a long time a gradual depletion of the reserve of myelocytes was obtained. These authors finally concluded that the activity of the bone-marrow was probably regulated by two factors:

1. A chemotactic factor influencing the discharge of cells from the bone-marrow into the peripheral blood. This factor they considered to be nucleic acid and its derivatives.

2. A growth-stimulation factor influencing the differentiation of the leucocytes into their various types. The nature of this factor is unknown.

Analogous observations in man are few and, although nucleic acid derivatives have been used for a number of years to combat serious leucopenia and agranulocytosis, nothing but clinical opinions—some favourable, some very unfavourable—have been available to assess the value of such treatment. The present paper is an attempt to provide real evidence on this problem in man, and this has been possible only since the development of the technique of intravital bone-marrow examination by sternal puncture. The author has studied extensively the morphology and functions of the normal bone-marrow by this technique, the work being published in his monograph of 1935. The classification of the granular leucocytes which he has used is chiefly that of Doan, but partly that of Ferrata (1933). Doan's classification of myelocytes is briefly as follows:

Type A—most primitive, few granules, many mitochondria, nucleus round or oval.

Type B—intermediate stage, nucleus oval.

Type C—most mature, numerous granules, few mitochondria, nucleus kidney or C-shaped with commencing lobulation.

Ferrata divides the myelocytes into three groups practically identical with Doan's A, B, and C types but with the following names: premyelocytes, myelocytes, and metamyelocytes. In considering the various cells the writer has also made use of the term 'rod-forms' or 'rod-cells'. These are equivalent to the German 'stab-cells', and were described by Schilling as 'a granular leucocyte containing a nucleus of rod-form often curved, and met with in a variety of toxic states'. The presence of these forms, and of cells with perfectly segmented nuclei is the basis of the well-known 'shift to the left' in the Arneth count or Schilling haemogram.

The author in his earlier work on the bone-marrow by the technique of sternal puncture distinguished two processes simultaneously at work: (1) the maturation of the granular leucocytes within the marrow, and (2) their discharge into the blood. He found that in normal marrow the mean percentage of metamyelocytes, rod-forms, and mature leucocytes was 47 per cent., while myeloblasts, premyelocytes, and myelocytes (see classifications of Doan and Ferrata) amounted to 18 per cent. He noted that in normal subjects the maturation process of the nucleus and of the granular protoplasm proceed simultaneously, and the barrier between the marrow and the circulating blood functions with great precision, preventing immature cells from reaching the peripheral blood to any great extent. Confirmation of these physio-

logical views was obtained by an extensive study of pathological material. In infections and other toxic processes affecting the bone-marrow, disturbances both of the maturation process and of the discharge into the blood takes place. The disturbance of maturation first shows itself by a relative increase of the myelocytes, later of the premyelocytes, and, in certain conditions, also of the myeloblasts. The graver the infection the earlier was the disturbance found and the more were the primitive cells increased. In conditions of very severe damage complete arrest of maturation was found, and this may occur at any stage prior to the metamyelocyte. In addition, a disturbance of the simultaneous maturation of the nucleus and of the granular protoplasm also ensued. The upset in the process of discharge of cells from the marrow into the blood-stream was clearly shown by the presence of immature forms of myeloid cells in the peripheral circulation.

The two essential phenomena may be combined in different ways. For instance, the peripheral leucocytosis in the circulating blood may not fully correspond to the alterations in the maturation process or to those in the mechanism of discharge from the bone-marrow. The so-called 'shift to the left' is mainly an indication of the relaxed control of the discharge, but also parallels in most cases the disturbance in the maturation process. A leucocytosis without 'shift to the left' corresponded as a rule to a fairly intact maturation process, while the 'shift to the left' showed both disturbed maturation and lack of control of discharge. Leucopenia without 'shift to the left' was found as a rule to be associated with a normal morphology of the bone-marrow, but when 'shift to the left' occurred an obvious disturbance of the maturation process of the myelocytes was found in the marrow.

The author used the method of sternal puncture described by Arinkin (1929) which makes available for examination only minute samples of marrow. He found that the reactions in the bone-marrow were the same in the sternum, the ribs, the vertebrae, and the innominate bone, so that the findings in the sternum may be considered as representative. The author's view of the functions of the marrow corresponds fairly closely with that of Sabin and Doan (1927), except that his conception of the maturation process is somewhat wider and includes the development of the myeloid cell from myeloblasts to mature leucocytes. Sabin and Doan confine their attention more closely to the output of mature leucocytes rather than metamelocytes and earlier forms.

Clinical Material

Forty-three patients have been examined, 42 at St. Erik's Hospital and one at the Seraphimer Hospital; 59 experiments in all have been carried out. The patients are divided into four groups:

1. Normal subjects, secondary anaemias, and mild infections, all without 'shift to the left' in the Arneth-Schilling count.

2. Normal subjects, secondary anaemias, and mild infections with a 'shift to the left'.

3. Severe acute infections, without anaemia or leucopenia, but with a pronounced 'shift to the left'.

4. Cases of pernicious anaemia in relapse or remission.

In addition, prolonged observations and injections have been carried out on a patient with tuberculosis coxitis showing slight secondary anaemia without a 'shift to the left'. The patients described as normal were average hospital patients suffering from ulcers, cardiac disease with slight failure, arteriosclerosis, and various forms of psychosis. The secondary anaemias were due to nephritis, cancer, infections, anaemia after haemorrhage, and some cases of essential hypochromic anaemia.

Experiments

General procedure. No change was made in the patients' diet, and they were kept in bed for the first day only; no liver or iron treatment was applied in any of the anaemias during the whole course of the experiments. Complete examinations of the blood and bone-marrow were made before and during the experiments, and the differential counts on the bone-marrow were carried out on 1,000 cells. In the figures only the bone-marrow cells which are of interest for the present investigation are referred to, under the terms myeloblasts, premyelocytes, myelocytes, metamyelocytes, rod-forms, mature segmented leucocytes, lymphocytes, and nucleated red cells. Further condensation in the figures has been obtained by pooling the myeloblasts, premyelocytes, and myelocytes into one group and the metamyelocytes and rod-forms into another. The normal values accepted are 18 per cent. for the primitive cells, 22 per cent. for the metamyelocyte group, 25 per cent. for segmented mature leucocytes, 20 per cent. for lymphocytes, and 12 per cent. for nucleated red cells. These values and the figures for the white cells of the peripheral blood, including the differential count, have been plotted in Figs. 1 to 7.

Nucleic acid preparations used. For the experiments sodium nucleinate and pentose nucleotide of different makes (Swedish, Nuclosin; American, Pentose Nucleotide; German, Pentosnucleotide) have been employed, and also adenine sulphate. The adenine compound, which, according to Jackson (1924), may form the major part of the nucleotide of human blood, was kindly supplied by Dr. E. Jorpes of the Department of Biochemistry of the Caroline Institute, Stockholm. The sodium nucleinate was given intramuscularly as a 10 per cent. solution in doses of 0.5 to 1.5 gm. Pentose nucleotide was injected intramuscularly in doses of 10 c.c., corresponding to 0.7 gm. Adenine sulphate was given intravenously as a 3 per cent. hot solution with a dosage of 1 gm. In all patients who received sodium nucleinate and pentose nucleotide, chill and fever occurred within four to twelve hours after the injection, the maximum temperature being 40° C. (104° F.), and the fever

in all cases had disappeared within twelve hours. Adenine sulphate did not produce a similar reaction. Following the injections the peripheral leucocyte count was studied every hour for fifteen hours, and the bone-marrow was examined in certain cases as often as five times during the same period. During the subsequent days the peripheral leucocyte count (fasting value) was followed every day for fourteen days, during which time the bone-marrow was examined at most three times.

Experimental results. The results are set out in Figs. 1 to 7. The upper curves represent the percentage composition of the sternal marrow cells. The lower curves represent the peripheral blood and give the percentage variation and the numbers of the white cells. The scale of the ordinate of the upper half is twice the scale of the lower half. Monocytes are omitted from the curves since these cells showed no changes whatever during the experiments. The same system has been used for all the curves.

Fig. 1. Control case. The number of leucocytes in the peripheral blood varied considerably during the twenty-four hours, but the fasting values varied only slightly. The differential count of the white cells during the entire experiment was almost constant both in the marrow and in the peripheral blood.

Fig. 2. Three normal cases of secondary anaemia without 'shift to the left' in the peripheral blood. In these cases injection of *sodium nucleinate* resulted in a slight reduction of peripheral white cells in the first hour followed by a leucocytosis reaching its height after seven to thirteen hours, persisting for several days and disappearing slowly. The increase consisted entirely of mature granular cells without young forms and persisted for twelve days after injection. A relative lymphocytopenia was present. In the bone-marrow a decrease of immature myeloid cells and an increase of mature granular leucocytes was evident. These changes reached their peak after nine hours followed by a rapid return to the original proportions. During the following ten days the bone-marrow showed no alteration from the normal in composition.

Fig. 3. Eight normal cases, two secondary anaemias, and one acute infection, without 'shift to the left' in the peripheral blood. After injection of *pentose nucleotide* a granular leucocytosis rapidly developed without 'shift to the left' and with relative lymphocytopenia. These changes reached their height six to nine hours after injection. In the bone-marrow again a decrease of immature myeloid cells and an increase of mature leucocytes was observed, the changes reaching a maximum seven to eleven hours after injection. Thereafter the bone-marrow rapidly returned to normal and showed no alteration during the following days.

Fig. 4. One normal and two secondary anaemias without 'shift to the left'. After injection of *adenine sulphate* changes were minimal in the bone-marrow and absent altogether in the peripheral blood.

Fig. 5. Four normal cases and five secondary anaemias with a 'shift to the left' in the peripheral blood. After *sodium nucleinate* slight leucocytosis

with relative lymphocytopenia developed with a maximum six to eight hours after the injection, but these alterations rapidly disappeared. In the bone-marrow slight increase of the mature granular cells and decrease in the immature myeloid cells took place, with a maximum at seven to eleven hours. Recovery to normal was rapid.

Fig. 6. Six normal cases, 11 anaemias, and two acute infections, all with regenerative changes in the peripheral blood. After *pentose nucleotide* rapid granular leucocytosis developed without increasing the 'shift to the left', and without lymphocytopenia, maximal in five to nine hours. These changes persisted for five days, after which the peripheral blood picture was normal. In the bone-marrow within six to nine hours marked increase of mature leucocytes with reduction of the earlier myeloid elements was observed. The bone-marrow picture, however, had returned to normal within twenty-four hours.

Fig. 7. One normal case and one secondary anaemia with a 'shift to the left'. After *adenine sulphate* few changes in the peripheral blood were noted, but premyelocytes and myelocytes increased in the bone-marrow to a maximum about seven hours after the injection.

In all the experiments so far described the changes are not greatly different from those already described in the literature. In the following experiments, however, the changes are different:

Fig. 8. Three severe acute infections with leucopenia and pronounced 'shift to the left' in the peripheral blood. After *pentose nucleotide* the composition of the peripheral blood was unchanged, except for possibly a slight reduction in the total number of white cells. The bone-marrow before the injection had already shown great alterations, with increase particularly of premyelocytes, but also of myelocytes. Both of these cell types increased further after injection, while the number of more mature cells diminished. These alterations again occurred with a maximum at eight to nine hours, and within twenty-four hours the bone-marrow picture was again identical with that when the experiment began.

Fig. 9. Two cases of pernicious anaemia in relapse. The results of injection of *pentose nucleotide* were practically negative both in the blood and bone-marrow. In the peripheral blood a moderate increase of granular cells and a moderate lymphocytopenia occurred.

Fig. 10. Three cases of pernicious anaemia in remission. Here injection of *pentose nucleotide* was followed by marked granular leucocytosis without 'shift to the left' within six to ten hours. Return to normal was rapid. In the bone-marrow the primitive myeloid elements decreased and the mature segmented leucocytes increased. These changes were maximal within eleven hours and had disappeared within two days.

Fig. 11. Two cases of pernicious anaemia in remission. *Adenine sulphate* injection brought about no marked changes in the peripheral blood, but in the bone-marrow the primitive cells decreased and the mature leucocytes were markedly increased to a maximum nine hours after injection.

Fig. 12. In one patient with secondary anaemia without 'shift to the left', repeated injections of *pentose nucleotide* were given; during the first four days 1.4 gm. was given daily, and from the fifth to the tenth day 0.7 gm. daily. Marked granular leucocytosis developed and was repeated after every injection during the four following days. Thereafter, for the remainder of the experiment the peripheral blood picture was not affected at all, except possibly for a slight increase in the white cells on the tenth day. In the bone-marrow decrease of myelocytes and metamyelocytes occurred after each daily injection, the changes being greatest from the sixth to the tenth days after the experiment commenced. The more primitive cells remained unaffected, just as after a single injection. Mature leucocytes were unaffected during the first day, but thereafter rapidly increased. By the fourteenth day a gradual return to normal in the bone-marrow picture was evident.

It may be added that in none of the whole series of experiments was any increase in mitoses or of cells in amitotic division observed in the bone-marrow. There was, however, particularly in certain cases, striking evidence of myeloid hypertrophy at the expense of the erythroblastic tissues. The normal ratio of myeloid to erythroblastic cells in the marrow may be taken as 75 to 25 per cent.; in some experiments the ratio reached 95 to 5 per cent.

Discussion

The results of the experiments may be divided into two parts:

I. Effects on the peripheral blood.

II. Effects on the bone-marrow.

I. *Peripheral blood.* (a) *Sodium nucleinate* caused a rapid leucocytosis in all the cases treated, maximal in six to twelve hours, and without initial leucopenia. There was no 'shift to the left', and the drug had no effect on the production of white cells in the marrow. It should be noted, however, that no cases of pernicious anaemia in remission and no severe acute infections were treated with this drug. An initial leucopenia, occurring within an hour after injection, has been noted by most authors, but was never seen in the present series. Bruce (1894), Doan (1926), Webb (1924), Wells (1917), and others have explained this initial leucopenia on the view that a temporary accumulation of leucocytes occurs in the large depots—lungs, spleen, and intestine. Others, such as Moshagen (1934), have inferred that an initial rapid destruction of leucocytes takes place. There is no reason to suppose that the purity of the sodium nucleinate injected accounts for this phenomenon.

(b) *Pentose nucleotide* caused a similar rapid granular leucocytosis without initial leucopenia in normal cases, secondary anaemias, and slight infections with or without 'shift to the left'. There was no effect, however on three cases of severe infection, and none on pernicious anaemia in relapse. During the remission or recovery stage of pernicious anaemia rapid leucocytosis occurred with both drugs.

(c) *Adenine sulphate* produced, in the few experiments, no changes in the peripheral blood at all.

II. *Bone-marrow.* (a) *Sodium nucleinate* hastened maturation of leucocytes, this being shown by an increase in mature cells and a decrease of myelocytes and metamyelocytes. Myeloblasts and premyeloblasts were unaffected.

(b) *Pentose nucleotide* produced in cases without previous marrow damage changes identical to (a), whereas in grave infections (Fig. 4) and in pernicious anaemia in relapse (Fig. 5) no such favourable effects were noticed.

(c) *Adenine sulphate*—few experiments and few changes of importance.

Thus it is seen that in these experiments both *sodium nucleinate* and *pentose nucleotide* produced changes in both blood and bone-marrow; but only if the bone-marrow had been previously intact and had not suffered from previous toxic changes with disturbed maturation of the cells. Such damage to the bone-marrow is seen both in infections and in pernicious anaemia in relapse. Neither of these drugs altered the control of discharge of cells from the bone-marrow to the blood. It appears, therefore, that as long as the bone-marrow has relatively intact stores of myelocytes, peripheral leucocytes can be produced and maintained in treatment. Otherwise, in severe infections and in relapses of pernicious anaemia the alterations in the peripheral blood become aggravated by leucopenia and pronounced 'shift to the left'.

Summary

1. The effects of *sodium nucleinate*, *pentose nucleotide*, and *adenine sulphate* on the peripheral blood and the bone-marrow have been studied in 59 experiments on 43 patients. The experiments with *adenine sulphate* are admittedly scanty.

2. The cases have been divided according to whether the white cells of the peripheral blood have been normal, increased, diminished, or with a 'shift to the left'.

3. Both *sodium nucleinate* and *pentose nucleotide* can induce a continuing peripheral neutrophil leucocytosis, with hastened maturation of the granular cells of the bone-marrow, but only if the bone-marrow has been previously undamaged.

4. If bone-marrow damage has previously occurred, in infections and in the relapses of pernicious anaemia, neither of these changes takes place.

5. The regulation of the maturation of the myeloid cells in the bone-marrow is discussed.

6. It is hoped that the experiments recorded have some practical bearing on the therapeutic use of nucleic acid derivatives in agranulocytosis. The importance of the previous state of the bone-marrow, in relation to the results obtained, is emphasized.

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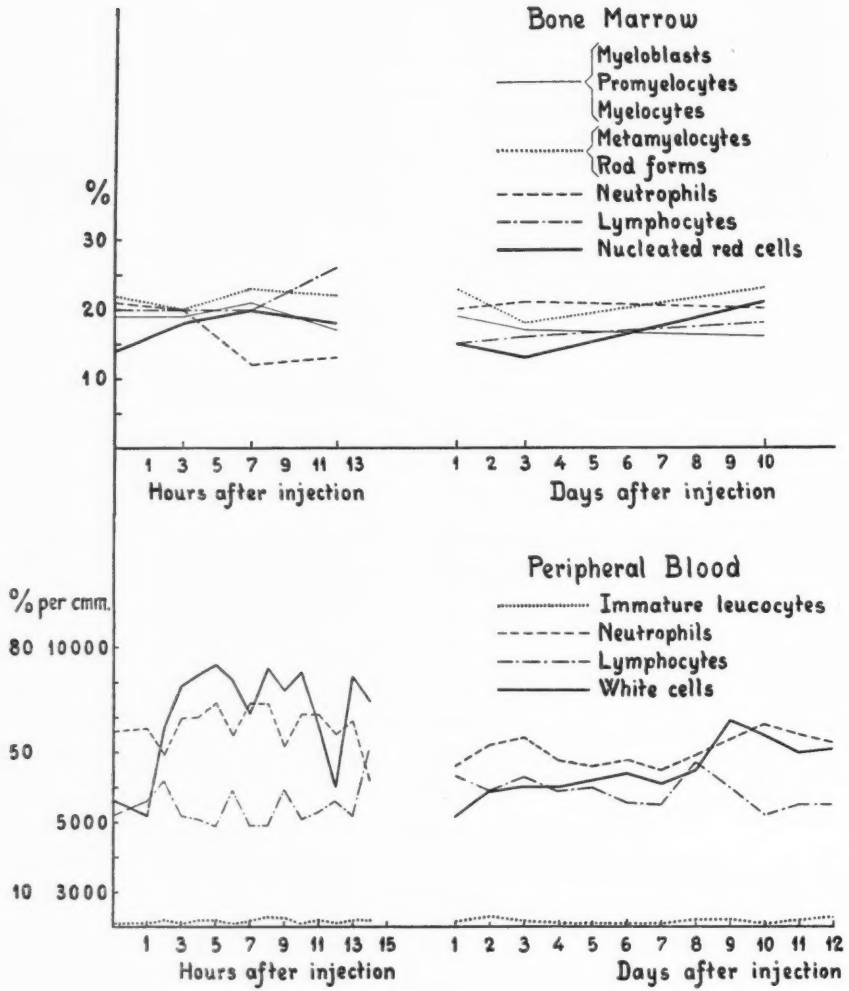


FIG. 1.

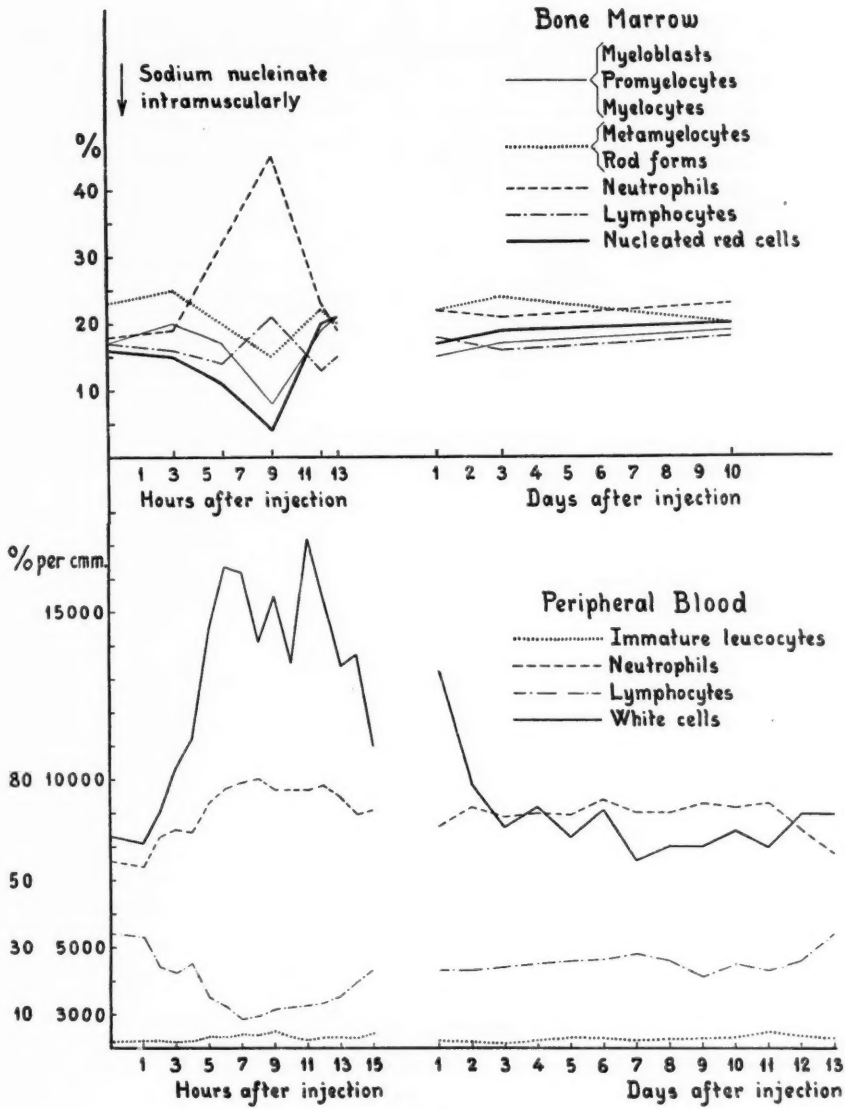


FIG. 2.

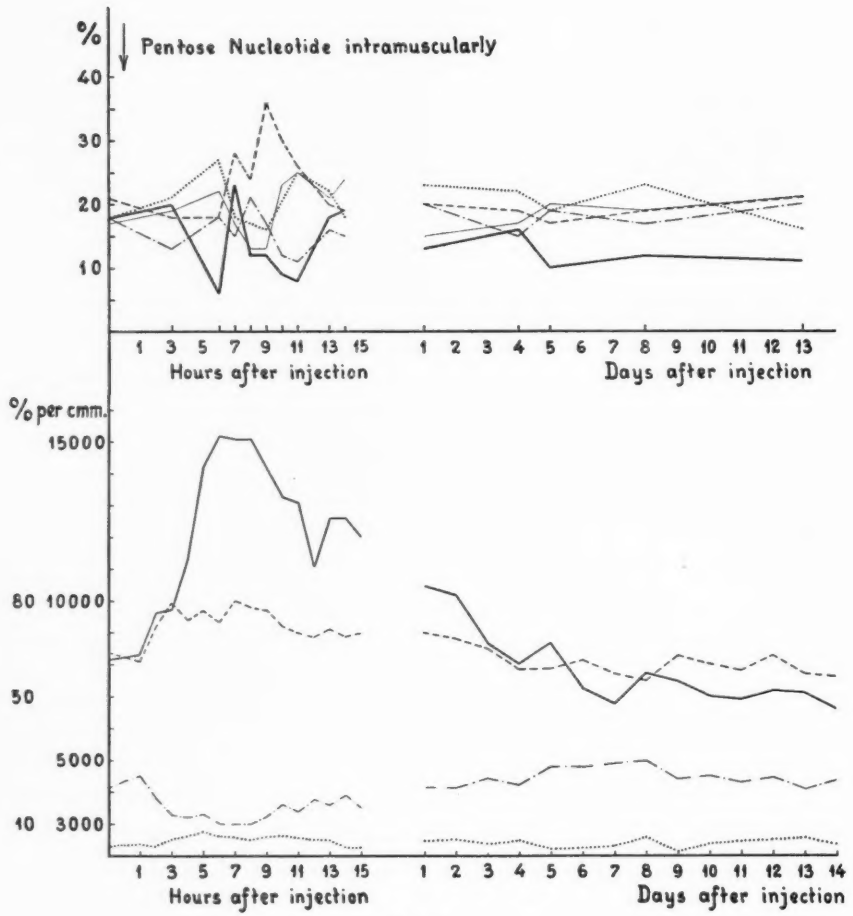


FIG. 3.

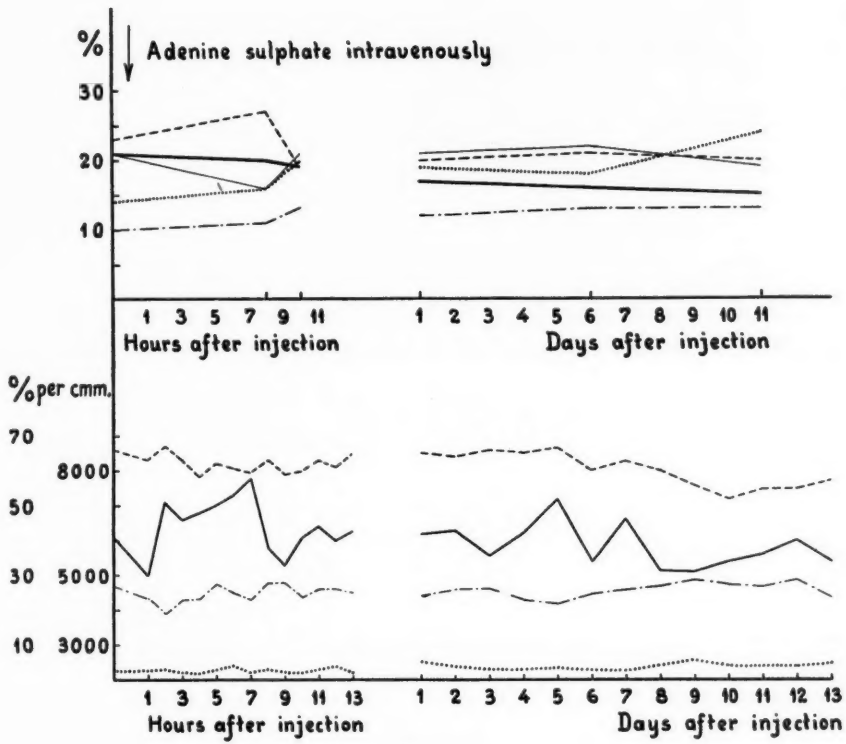


FIG. 4.

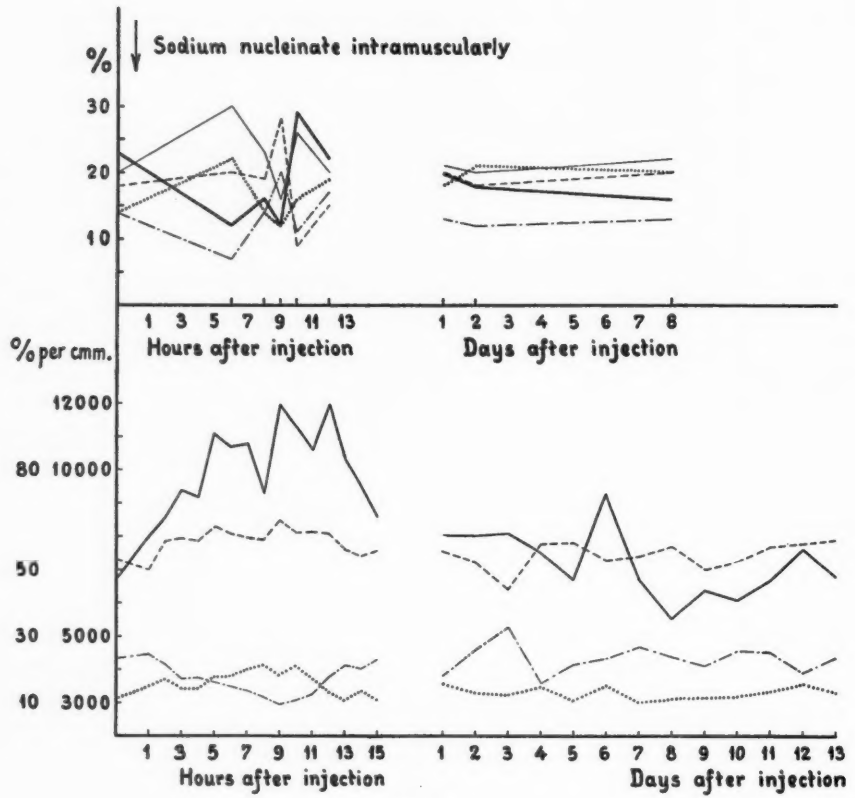


FIG. 5.

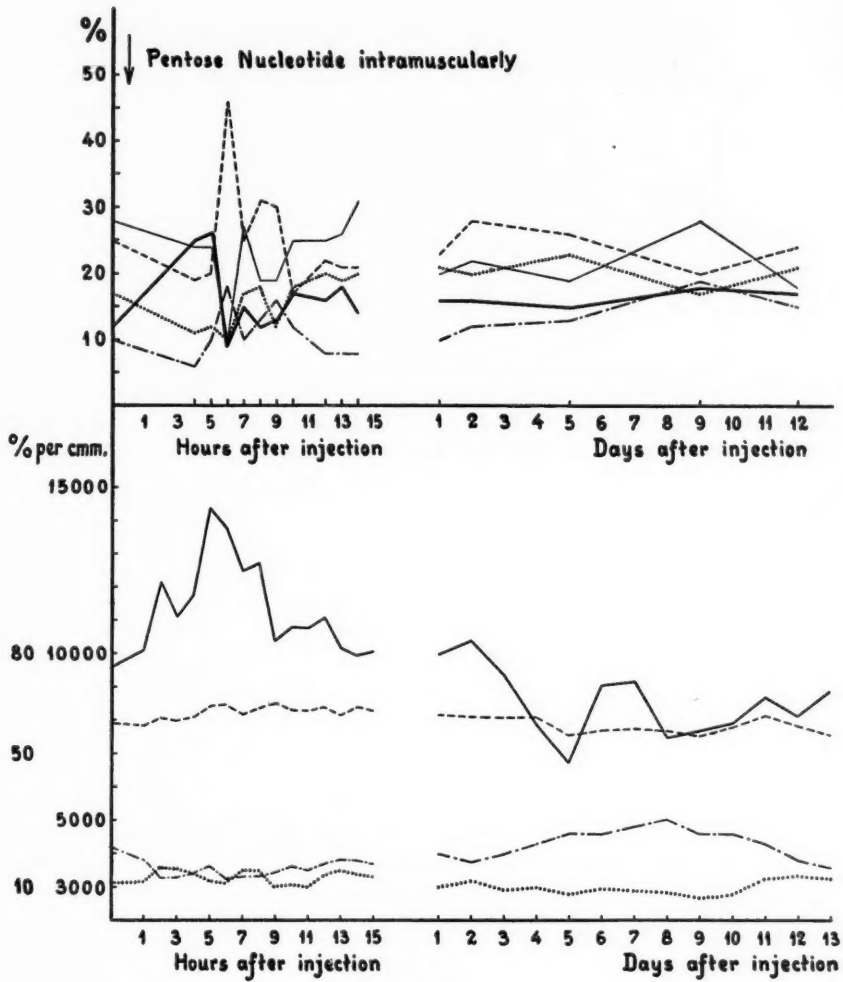


FIG. 6.

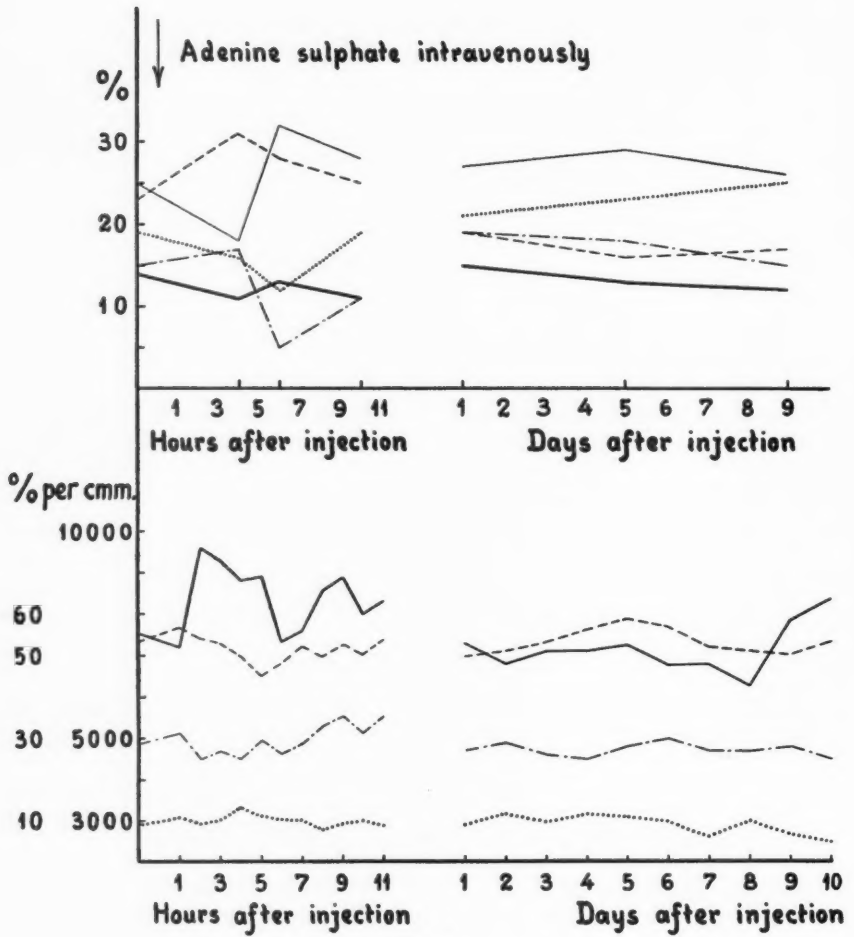


FIG. 7.

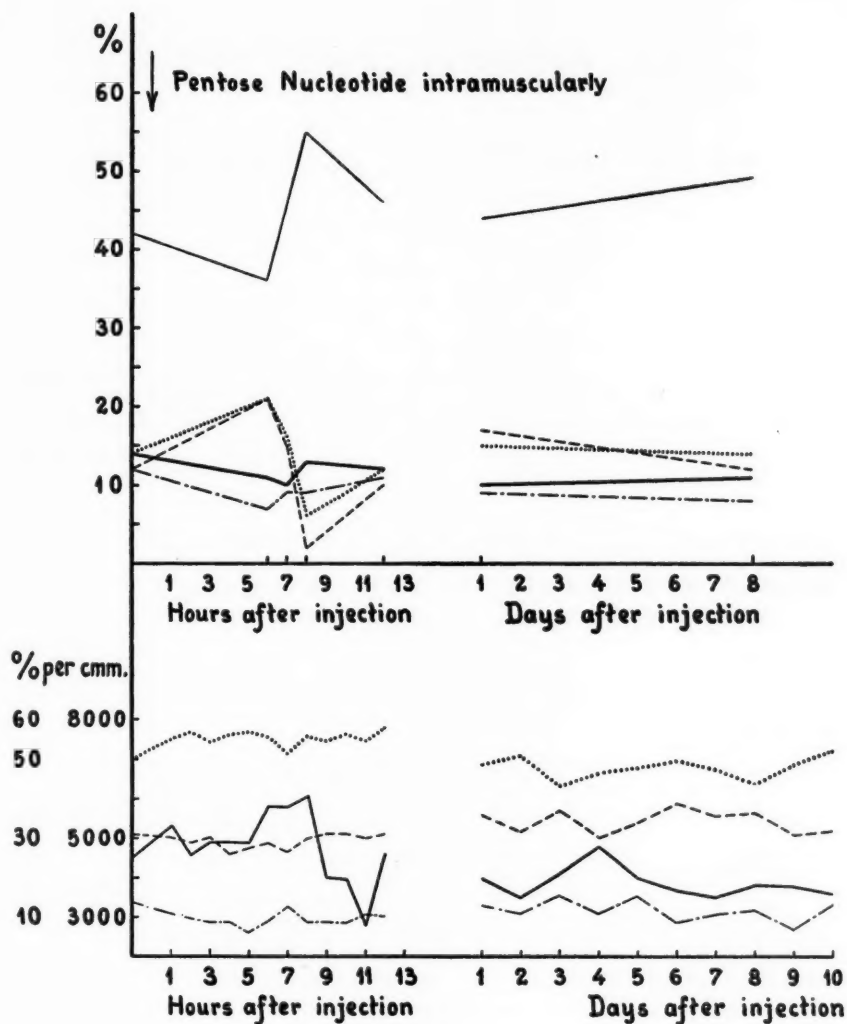


FIG. 8.

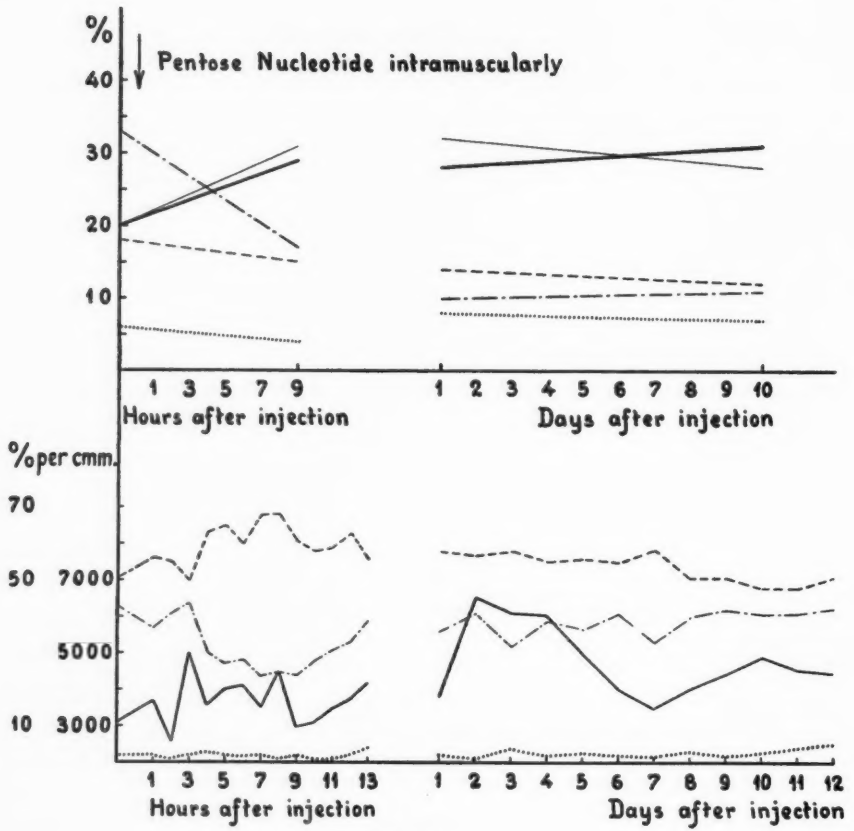


FIG. 9.

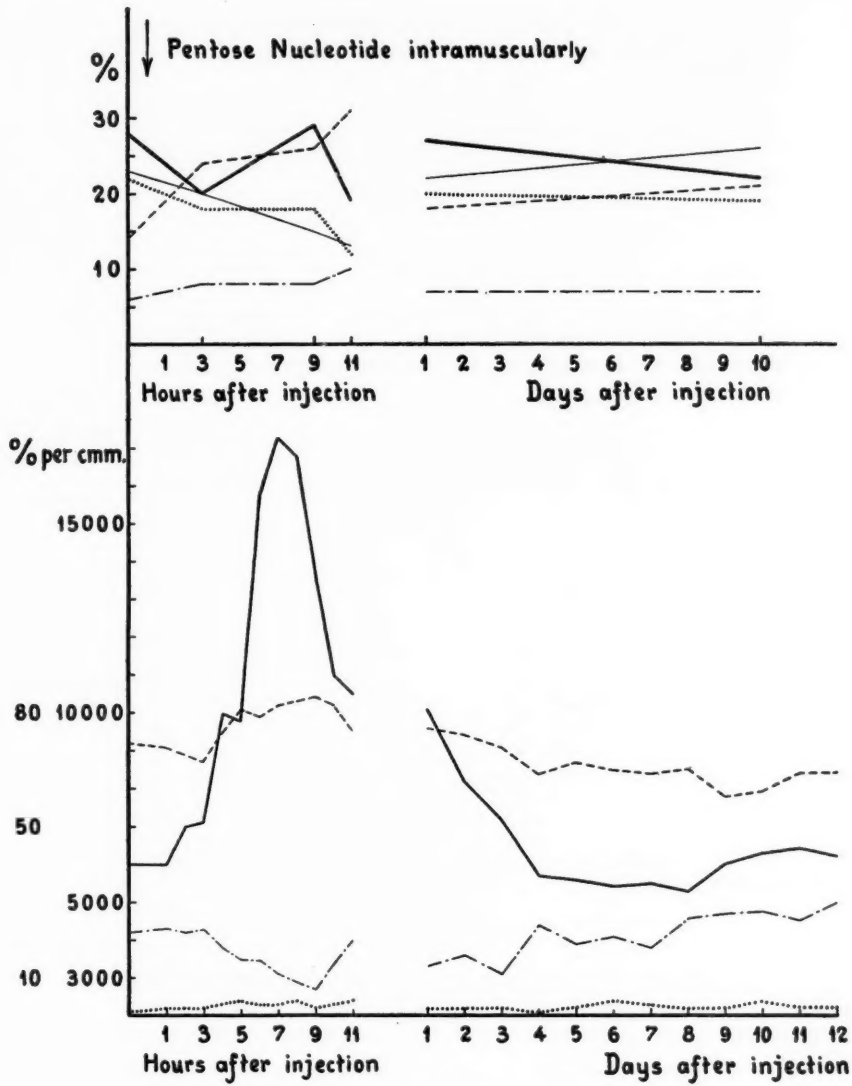


FIG. 10.

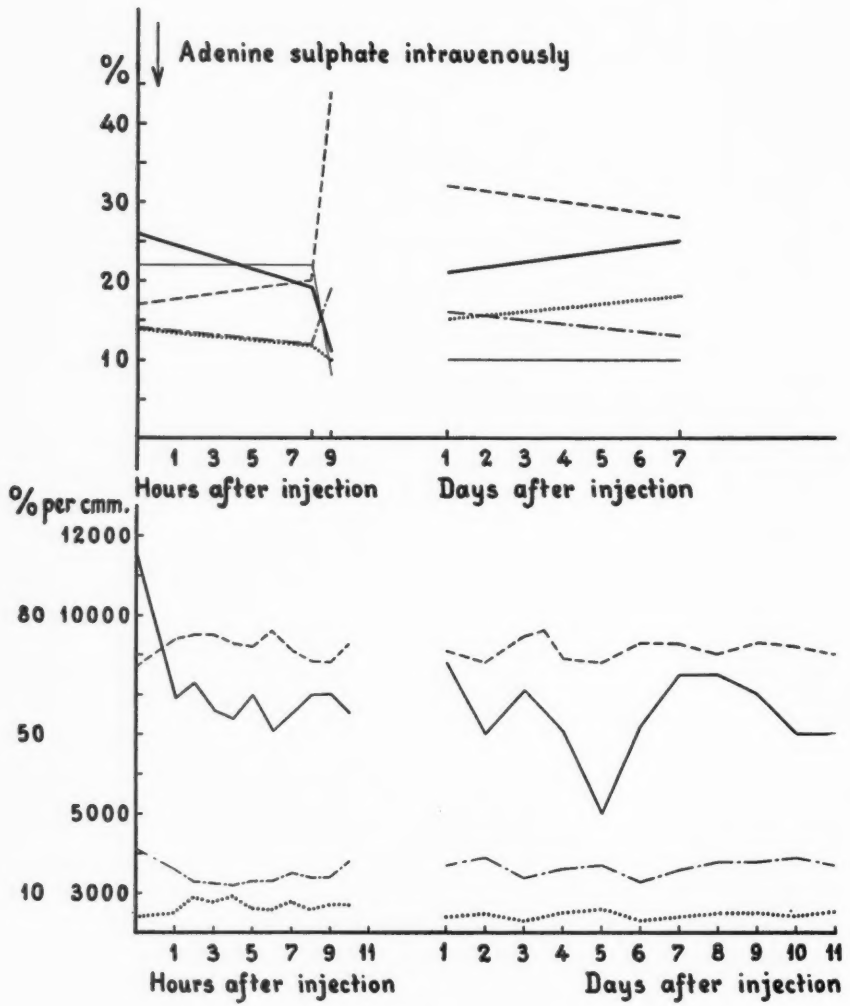


FIG. 11.

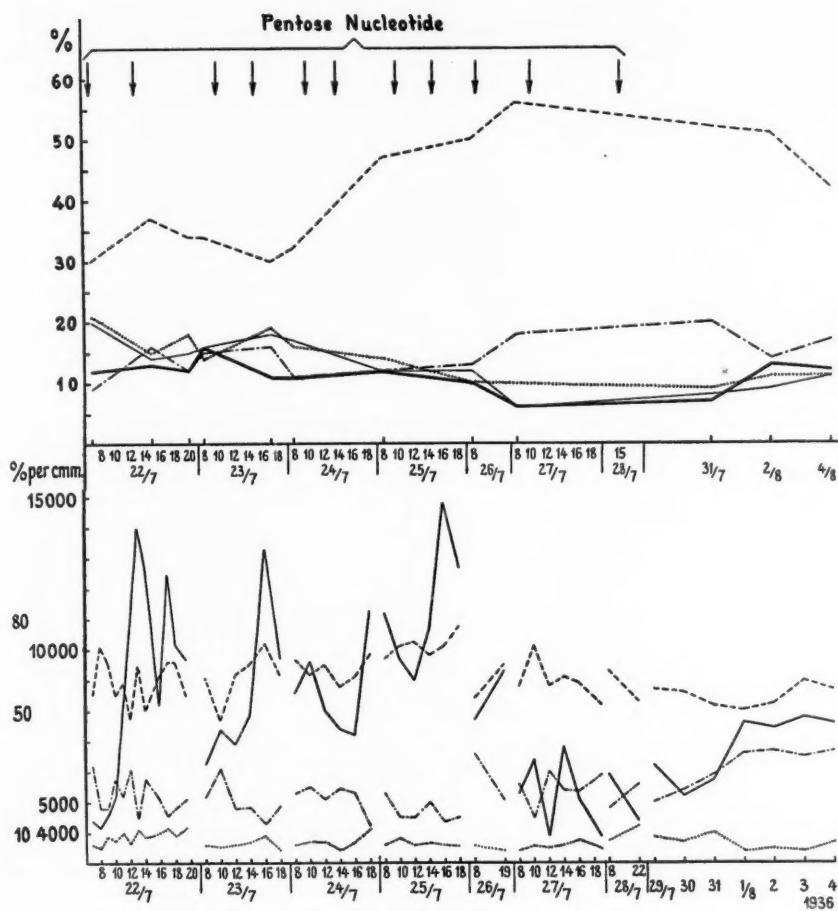
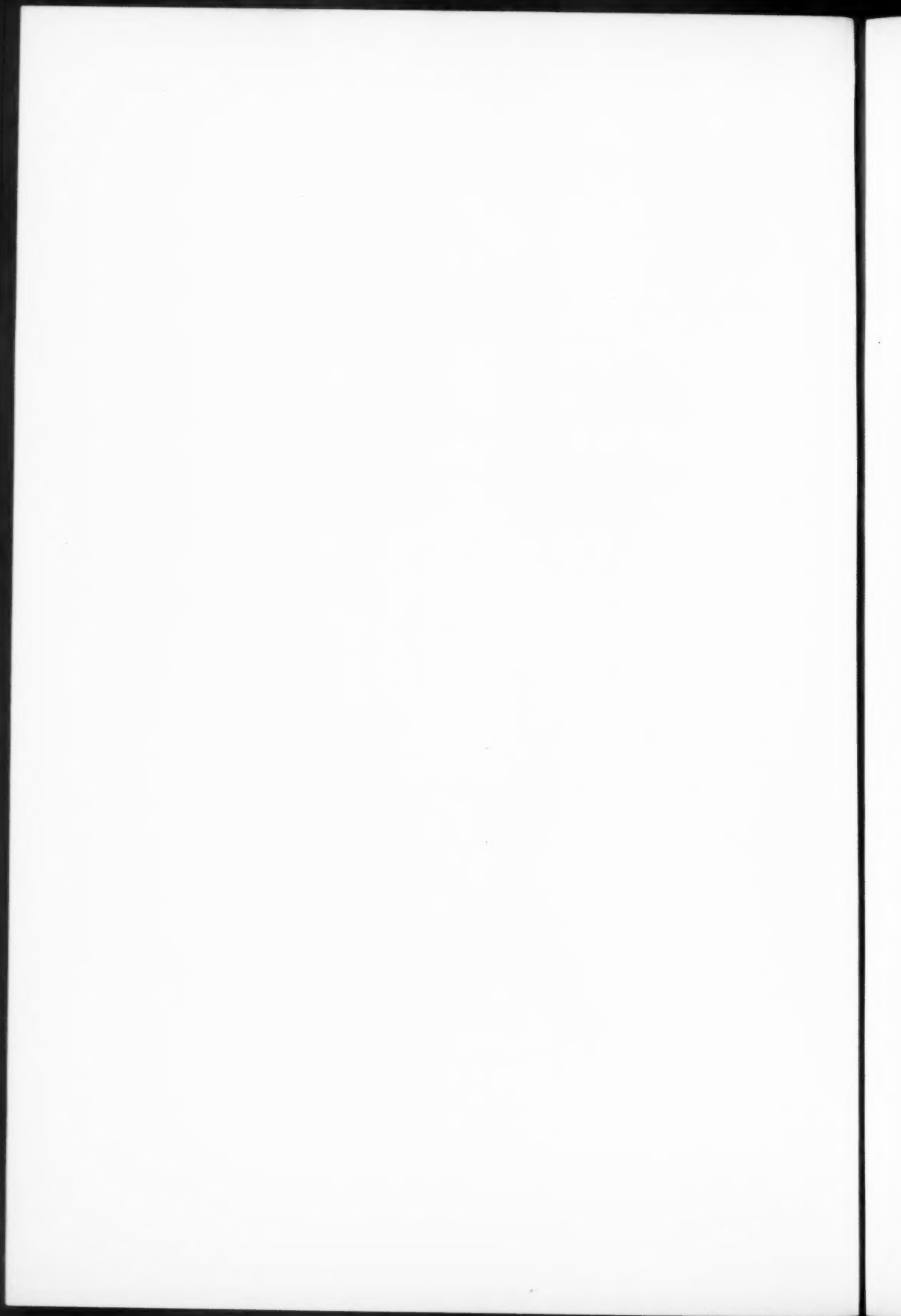


FIG. 12.



ATYPICAL HAEMOLYTIC ANAEMIAS¹

BY F. GRAHAM LESCHER AND GLADSTONE R. OSBORN, WITH
TECHNICAL ASSISTANCE FROM J. J. G. BATES

(From the Medical and Pathological Departments of the Derbyshire
Royal Infirmary)

With Plates 19 to 21

Introduction

THE haemolytic anaemias, or, as Parsons (1938) prefers to call them, 'the erythronoclastic anaemias', form a somewhat unsatisfactory group, since there is no very clear and accepted standard as to what constitutes clinical haemolysis. Even when the occurrence of haemolysis has been accepted, there is seldom direct evidence of its presence, as it rarely occurs in the blood-stream itself. The clinical criteria of haemolysis are—anaemia, often severe; rarely, haemoglobinaemia or haemoglobinuria; a stationary or falling red-cell count, with signs of immaturity of the erythrocytes (i.e. a raised and sustained reticulocytosis); and an elevated serum bilirubin, with an indirect positive van den Bergh reaction and an increase in urobilin excretion. When haemolysis takes place in the blood-stream itself, haemoglobinaemia, haemosiderinuria, and 'ghost' cells are found.

We have recently had the opportunity of studying in detail two uncommon examples of haemolytic anaemia, and of comparing sections of the spleens with others of a somewhat similar clinical type. There is some difficulty in classifying the first case, but it appears to belong to the group described by Davidson (1932) and Davidson and Fullerton (1938) as 'macrocytic haemolytic anaemia'. The second case is a macrocytic haemolytic anaemia with paroxysmal haemoglobinuria, approaching, though differing in some respects from, the syndrome described by Marchiafava (1911, 1931) and by Micheli (1931).

Case 1. Macrocytic haemolytic anaemia. A married woman, aged 55 years, was seen by one of us (F. G. L.) in April 1937, on account of progressive weakness, anaemia, and jaundice.

History. About six months previously she had begun to lose strength, and to suffer from dyspnoea on exertion, palpitations, increasing pallor, and jaundice. The stools had never been clay-coloured. The tongue had been sore for a few weeks. Her condition was deteriorating in spite of repeated parenteral injections of a potent liver extract.

Examination. She was very thin. Cerebration was good and she took a cheerful view of her condition. The temperature chart showed a moderately fluctuating pyrexia, a quickened respiration, and increased pulse-rate. She was very anaemic, though this was partially hidden by the marked jaundice. There was a symmetrical enlargement of the thyroid gland, but no evidence of thyrotoxicosis was found. Marked atrophy of the papillae of the tongue was

¹ Received May 17, 1939.

TABLE I
Examinations of the Blood. Case 1. (*Macrocytic Haemolytic Anaemia*)

| | Dates: | | | | | | | | | | | |
|--|-------------------|------------|------------|--------------|------------|--------------------------|--------------------------|--|--|--|--|----|
| | 2.4.37 | 12.4.37 | 20.4.37 | 4.5.37 | 13.5.37 | 28.5.37 | 4.10.37 | | | | | |
| Hb. (per cent.) | 42 | 40 | 47 | 45 | 38 | 52 | 102 | | | | | |
| R. B. C. per c.mm. (in millions) | 1.5 | 2.0 | 1.4 | 2.1 | 1.0 | 2.1 | 5.0 | | | | | |
| Colour index | 1.4 | 1.0 | 1.6 | 1.1 | 1.8 | 1.2 | 1.0 | | | | | |
| Diameter of R. B. C. (halometer) | 8.6 μ | — | 8.6 μ | — | — | — | — | | | | | |
| W. B. C. per c.mm. | 16,000 | 7,400 | 7,600 | 9,700 | 25,000 | 7,900 | 9,700 | | | | | |
| Neutrophil polymorphs. per cent. | 70 | 70 | 48 | 84 | 69 | 75 | 26 | | | | | |
| Eosinophil polymorphs. per cent. | 0 | 0 | 6 | 1 | 0 | 2 | 2 | | | | | |
| Old metamyelocytes per cent. | 10 | 0 | — | 0 | 12 | — | — | | | | | |
| Lymphocytes per cent., and per c.mm. | 9%; 1,440 | 26%; 1,224 | 34%; 2,584 | 10.5%; 1,020 | 12%; 3,000 | 15%; 1,185 | 56%; 5,432 | | | | | 33 |
| Monocytes per cent., and per c.mm. | 5%; 800 | 4%; 296 | 12%; 912 | 4.5%; 437 | 7%; 1,750 | 5%; 395 | 16%; 1,552 | | | | | 36 |
| Anisocytosis | Moderate | Moderate | Moderate | Moderate | Moderate | Less | None | | | | | |
| Poikilocytosis | Moderate | Moderate | Moderate | Moderate | Moderate | Less | None | | | | | |
| Reticulocytes per cent. of R. B. C. | 90 | 50 | 60 | 50 | 80 | 7 | Less than 1% | | | | | |
| Megaloblasts per cent. | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | | | |
| Normoblasts per cent., and per c.mm. | 9.5%; 1,520 | 2%; 150 | — | 2%; 200 | 5%; 1,250 | 0 | 0 | | | | | |
| Punctate basophilia | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | | | | |
| Van den Bergh reaction | Indirect positive | — | — | — | — | Slight indirect positive | Slight indirect positive | | | | | |
| Bilirubin | 3.9 units | — | 3.9 units | 10.6 units | 13.2 units | — | — | | | | | |
| Fragility range per cent. saline, R. B. C.'s | 0.5-0.35 | — | 0.5-0.35 | — | — | — | 0.4-0.35 | | | | | |

present. There were several retinal haemorrhages. The heart was dilated, and the blood-pressure was 90/55. The spleen was felt, a hand's breadth below the costal margin, but the liver was not palpable. The lymphatic glands were not enlarged. There was slight oedema of the ankles. The next day she was removed to a nursing home for further study. Examinations of the blood were commenced (Table I and Fig. 1). The first blood count showed a profound anaemia, together with immaturity and an

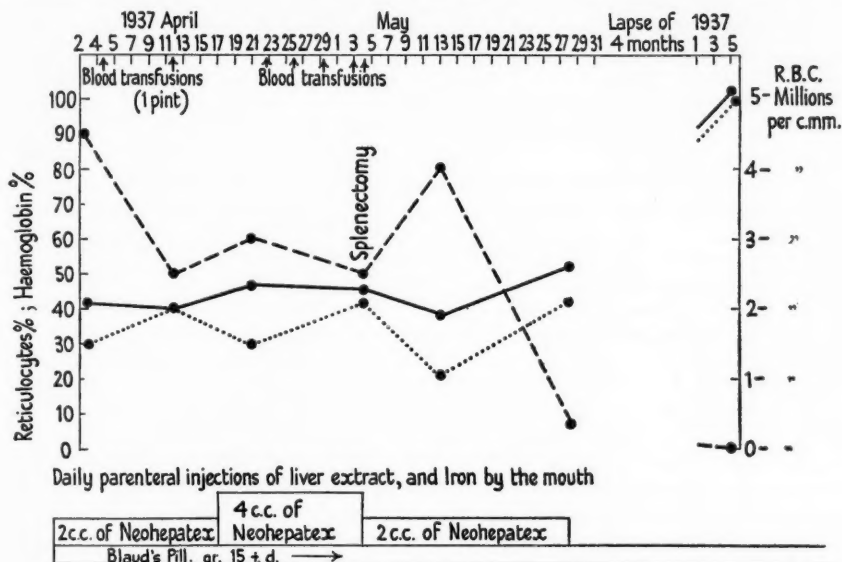


FIG. 1. Graph showing the results of blood examinations in Case 1 (macrocytic haemolytic anaemia).

— = Haemoglobin per cent.
 - - - - - = Reticulocytes per cent.
 = Red blood-cells in millions per c.mm.

increase in diameter of the erythrocytes (8.6μ halometer reading). There was a leucocytosis. The outstanding feature, however, was the high proportion of reticulocytes—90 per cent., the highest we have ever seen. At first the blood contained 3.9 units of bilirubin, but later the amount increased to over three times this value. The blood-serum was unaltered in colour. The fragility of the red cells was slightly increased. The Wassermann and Kahn reactions were negative. A fractional test meal after injection of histamine showed an achlorhydria with a low combined acidity. The stools were normal in colour and consistency. The urine was concentrated, and contained urobilin in excess, but no bilirubin. There was a trace of albumin, but no red cells, casts, pus, haemoglobin, or haemosiderinuria were found.

Treatment and progress. Daily injections of a potent liver extract were continued, together with large doses of iron. On April 4 she was given a blood transfusion, two hours being taken to transfuse one pint of citrated blood (after careful cross-matching) from a donor of the same group, without any abnormal reaction following. Numerous authors, including Dawson (1931), Davidson and Fullerton (1938), and Sharpe and Davis (1938), have referred to the dangerous and even fatal reactions which may follow blood

transfusion in cases of haemolytic anaemia, even when all the tests for compatibility have been carried out with satisfactory results. Dameshek and Schwartz (1938 *a*) have reported that sera from three cases of haemolytic anaemia were active in haemolysing red cells of all groups. Dawson (1931) and Doan, Wiseman, and Erf (1934) consider that transfusion in these cases is contra-indicated as well as unnecessary. However, if care is taken to choose a donor of the same group as the patient, to cross-match accurately by testing the donor's red cells with the recipient's serum and even vice versa, and to use reliable typing sera of high titre, it is not necessary to abstain from or to restrict the transfusion to a small amount (Lescher, 1937). The blood should be fresh, and it must be given very slowly by a properly regulated drip apparatus. Reactions are then less liable to occur, and the transfusion can be stopped (sometimes with success) if signs of incompatibility arise.

For a few days following the first transfusion the patient improved. Later, her condition again gave rise to anxiety. Professor Leonard Parsons saw her in consultation, and agreed that the spleen should be removed. In order to do this with greater safety, further efforts were made to raise the blood-count level by repeated drip transfusions, with some improvement. On May 4, Mr. Gerard Dyke removed the spleen and one accessory spleen, a blood transfusion being given both before and directly after the operation. During the next nine days her condition continued to be fairly satisfactory. A blood crisis then occurred, and once more she became desperately ill. A week later, however, she started to improve. The reticulocytes dropped to 7 per cent., and the red cells began to increase in number. By the end of the month she was well enough to be sent to her home in the country for convalescence. In the following July and October she was seen again. Her general condition had greatly improved, the jaundice having almost disappeared and the anaemia being definitely better. An examination of the blood gave normal figures, with a reticulocyte count of less than 1 per cent. The fragility of the red cells was normal. The jaundice and the soreness of the tongue had disappeared. We have heard recently (June 1939) that she continues to be perfectly well and is able to lead a strenuous life quite satisfactorily.

Description of the spleen. Weight, 20 oz. Capsule, thin. Cut surface, deep red. Microscopically, the Malpighian bodies are numerous and large, and there is some variation in their structure (Plate 19, Fig. 4). The smaller ones are composed of small lymphocytes. In many the central zones stain more deeply. The larger ones have a prominent 'germinal centre' composed of large reticulo-endothelial cells with clear vesicular nuclei. Mitotic figures are seen in a few of the larger centres. These changes are very similar to those found in thrombocytopenic purpura, which is notable in view of the excellent operative results in this condition. The littoral cells of the pulp are similar in structure and in iron content to those of typical acholuric jaundice, but the sinusoids are not so well filled. Erythrophagocytosis is present, but not prominent (Plate 19, Fig. 5.). The accessory spleen shows marked differences in structure, and should be regarded as a haemolymph gland. Follicle formation is its main feature. The follicles number up to 12 per low-power field, and are composed mainly of small lymphocytes. A few, however, have centres formed of larger reticulo-endothelial cells, similar to those found in the spleen itself. The pulp is composed of lymphoid sinuses with hyperplastic lining cells, in which are large numbers of red blood-cells. No iron pigment is seen.

Discussion of Case 1. At first sight there seemed to be some evidence of pernicious anaemia, but on clinical and haematological grounds there were conclusive reasons against this. The spleen was too large, and the reticulocytes too numerous. In pernicious anaemia, during the first few days of adequate treatment there is an increase in the reticulocyte count, but it is never so great as that found in this case. The extent of the reticulocyte response has been shown by Minot, Cohn, Murphy, and Lawson (1928) to be proportional to the depression in the number of erythrocytes. This increase, however, is only temporary, the number of reticulocytes falling within a few days, when the number of the erythrocytes starts to rise. A persistently raised reticulocyte count and low red-cell count are incompatible with pernicious anaemia. Leucocytosis, also, does not occur in this disease unless some infection is present. Again, in pernicious anaemia the amount of bilirubin in the blood is increased, but never to the extent found in some of the examinations of our patient, e.g. 10.6 and 13.2 units. Finally, the therapeutic test of giving a potent liver extract in adequate amounts over a suitable period failed to cause any improvement.

Acquired acholuric jaundice of the type described by Widal, Abrami, and Brulé (1908) is a somewhat vague syndrome, differing from the congenital form in several ways. Often it is more severe, the mortality rate is greater, there is no familial history, and frequently the spleen is smaller. The diameter of the red cells may be increased, and this may be so marked that the blood picture can resemble closely that found in pernicious anaemia (Kremer and Mason, 1936). Spherocytosis is generally less, or even absent. The fragility of the erythrocytes may be normal (Gänsslen, 1922, 1925; Dawson, 1931), but unless a reliable quantitative test is used, negative results are not of so much value. It is recognized, however, that the classification of acholuric jaundice into two groups, 'congenital' and 'acquired', is by no means accurate. Therefore, Thompson (1936) and Whipple (1937), after analysing the cases in the clinic for diseases of the spleen at the Presbyterian Hospital, New York, have divided haemolytic jaundice into two major groups, the 'typical' and the 'atypical'. In the former there are definite diagnostic criteria—a chronic disease of long duration and of relative mildness, with acute exacerbations; chronic, variable jaundice; anaemia, with evidence of blood-regeneration; and splenomegaly. In all cases of typical haemolytic jaundice the blood contains spherical microcytes, which they believe are pathognomonic. In atypical haemolytic anaemias, spherocytosis does not occur. The first signs of disease of either group may appear at any age, and a familial history may be present or absent without affecting the diagnosis. Thompson and Whipple consider, therefore, that the subdivision into the 'congenital' and 'acquired' types is no longer valid. The atypical group of haemolytic anaemias is, they agree, heterogeneous. In some cases the aetiological cause is known, in others none can be found during life or on post-mortem examination.

It is considered, generally, that the underlying abnormality of acholuric

jaundice is in the red cell. Doan, Wiseman, and Erf (1934) have found that the erythrocytes from two cases of typical acholuric jaundice were haemolysed when suspended in the plasma of normal subjects. This did not happen if red cells from a control were suspended in the plasma of the patient. But Dameshek and Schwartz (1938 *a, b, c*) claim that all haemolytic anaemias are due to the activity of haemolysins. In three cases of this disease they have found haemolysins of unusual activity which have failed to correspond to any described hitherto. They consider that spherocytosis represents an alteration in the mature red cell, brought about by various types or titres of haemolysin. The increased fragility of the red cell as the cause is not, however, accepted by all. Wiseman (1935) is of the opinion that the spleen is the organ at fault. Thompson (1936) considers that the spherical cells are removed selectively from the general circulation by the spleen and that their destruction takes place in that organ. Yet, increased fragility of the red cells, without spherocytosis, has been reported (Dyke and Young, 1938; Kremer and Mason, 1936). Vaughan (1936) has suggested that there may be some derangement of metabolism, due to a deficiency of an essential factor which affects haemopoiesis, but no proof of this is given. Maizels (1936) has produced some evidence of an abnormality in the chemical constitution of the red cell itself. Lederer (1925, 1930) has described an acute type of haemolytic anaemia in which he thinks that infection is the primary aetiological factor.

It is universally agreed that splenectomy is effective in typical (spherocytic) acholuric jaundice. In cases of the atypical (non-spherocytic) haemolytic anaemia, where the causal factor is known, e.g. hepatic disease, lymphadenoma, some chronic infections, or neoplasms, removal of the spleen would, of course, be useless. When, however, no cause can be found in the latter type, there is a difference of opinion. In four of Thompson's (1936) cases, splenectomy was performed, but only one improved. He, Whipple (1937), and Dyke and Young (1938) consider that splenectomy is contra-indicated and of doubtful value in atypical haemolytic anaemia, but this is not the opinion of many other writers, including ourselves. Successful results after splenectomy in these cases have been reported by Davidson (1932), Davidson and Fullerton (1938), Wilkinson and Israëls (1935), Kremer and Mason (1936), Dameshek and Schwartz (1938 *c*), Dyke and Young (1938), and by ourselves. From an analysis of the structure of the spleens from 11 cases of atypical haemolytic anaemia, and from a comparison of the clinical histories, we have found that improvement after splenectomy is likely to take place if the spleen corresponds materially in structure to that of typical acholuric jaundice or of thrombocytopenic purpura (Lescher and Osborn, 1939).

The Marchiafava-Micheli syndrome. Judging from the small number of cases on record, about 30 in all, some of which have been reported so imperfectly that the true condition can only with difficulty be recognized, the Marchiafava-Micheli syndrome is rare. Yet, it is possible, as Scott,

Robb-Smith, and Scowen (1938) have suggested, that minor cases do occur in which haemolysis is neither sufficiently intense nor rapid enough to produce haemoglobinuria, and thus they may pass unrecognized. Therefore, in all cases of haemolytic anaemia the blood-plasma should be examined for haemoglobin or its derivatives, and the urine for the presence of haemosiderin. Rosenthal (1932), Witts (1936), and Hamburger and Bernstein (1936) have reviewed the clinical aspects of this syndrome. The last-named have collected 21 cases from the literature and have added two of their own. Other cases have been reported by Witts (1936), Ham (1937), Brulé, Hillemand, and Gaube (1937), Dacie, Israëls, and Wilkinson (1938), and Scott, Robb-Smith, and Scowen (1938).

It is chiefly males in the third or fourth decade who are affected. There is no familial history, and up to the present time no evidence has been brought forward that any disease, including syphilis, predisposes towards it. The clinical picture of the syndrome is distinctive. The essential feature, on which all the other characteristics depend, is the constant intravascular haemolysis. This is slow, except during a crisis, and the increased amount of bilirubin is within the excretory capacity of the hepatic cells, provided they are functioning with efficiency. But, when haemolysis is so rapid that the conversion of haemoglobin into bilirubin cannot take place quickly enough, then the amount of haemoglobin or its derivatives rises above the renal threshold which, as Lichty, Havill, and Whipple (1932) have shown, exists for haemoglobin.

The jaundice is probably due to the effect of the general reaction and of the anaemia on the liver (Witts, 1936). Haemosiderinuria was described first by Marchiafava (1931). Owing to the continuous intravascular haemolysis, iron pigment is excreted constantly in the urine, even in the absence of haemoglobinuria.

The anaemia is macrocytic and hyperchromic, without spherocytosis. Signs of stimulation of the bone-marrow are generally present. Myelocytes are rarely seen. The mean corpuscular volume is said to be normal, though Hamburger and Bernstein (1936) and Scott, Robb-Smith, and Scowen (1938) have found it to be increased. The coagulation and bleeding-times are stated to be normal, but Montagni (1921) has found prolonged coagulation time and increased viscosity of the blood. The fragility is usually within normal limits, but if a quantitative method of estimation has been used, some increase has been found. During a crisis the neutrophil cells and platelets may fall to a low level; later there may be a leucocytosis and thrombocytosis (Witts, 1936). The course of the disease is protracted, and terminates in death, generally from venous thrombosis, but sometimes from some intercurrent infection, or as a result of splenectomy.

Case 2. Marchiafava-Micheli syndrome. A labourer, aged 39 years, was admitted to hospital on February 24, 1938, complaining of general weakness and of passing 'dark water' periodically.

History. Ten years previously, after returning home from work on a mild

day in winter, he had had an attack of shivering and abdominal pain, and began to pass 'black' urine. Three months later, after a walk on a cold day, he again noticed that his urine was 'black'. This cleared up in a few days. During the previous ten years he had suffered from six similar attacks. These were no worse in the night than during the day. He had never noticed that cold or exertion brought on an attack, but one had occurred shortly after an injection of liver extract.

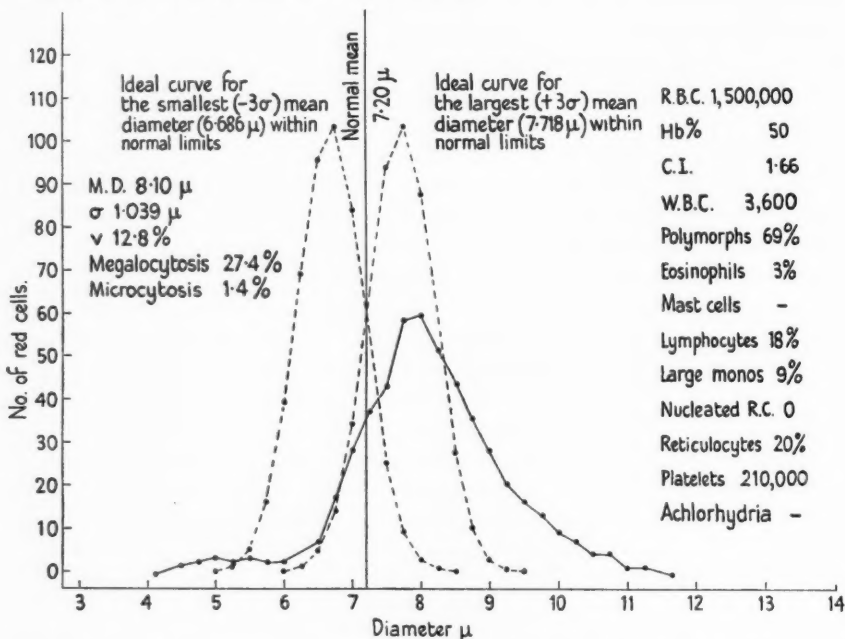


FIG. 2. Case 2 (Marchiafava-Micheli syndrome). Red-cell diameter distribution curve (Price-Jones).

Past and family history. He came of sound stock, and none of his relatives had at any time suffered from jaundice or anaemia. His previous medical history was uneventful. He denied syphilis. There was no history of the taking of drugs.

Examination. He was a well-nourished man, though pale, with a yellow tint of the skin and sclerae. Three pigmented black patches were found on the buccal mucous membrane. The firm, smooth edge of the spleen was felt, about two fingers' breadth below the costal margin. There was no enlargement of the liver or lymphatic glands. Nothing abnormal was discovered in the nervous system; the optic disks and retinae looked natural. The lungs were clear. Examination of the cardiovascular system revealed nothing abnormal. There was no clinical evidence of aortitis. The blood-pressure was 130/85. An electrocardiogram showed no abnormality. There was no evidence of vasomotor disturbance. There was no sign of a past chancre. Immersing the arms in ice-cold water failed to produce haemoglobinuria. Radiographs of both kidneys showed no shadows which might have been due to deposits of iron. The urine was orange in colour and the diurnal output was within normal limits; albumin was present invariably,

TABLE II
Examinations of the Blood. Case 2 (Marchiafava-Micheli Syndrome).

| Dates: | 4.2.38 | 24.2.38 | 4.3.38 | 19.3.38 | 30.3.38 | 6.4.38 | 20.5.38 | 17.6.38 | 5.7.38 | 12.7.38 | 13.7.38 |
|---|--|-----------|--------|-----------|---------------------------------------|---------|------------|-----------|-----------|---------|-----------|
| Haemoglobin per cent. | 55 | 60 | 55 | 55 | 52 | 45 | 55 | 50 | 50 | 45 | 60 |
| R. B. C. per c.mm. (in millions) | 2.6 | 2.5 | 2.5 | 2.4 | 2.0 | 2.0 | 2.0 | 1.5 | 2.5 | 2.1 | 2.5 |
| Diameter of red blood cells (halometer) | 7.6 μ | 7.4 μ | — | — | — | — | 7.32 μ | 7.5 μ | 8.0 μ | — | 8.0 μ |
| W. B. C. per c.mm. | 6,500 | 5,400 | 3,700 | 3,000 | 4,100 | 2,200 | 4,100 | 3,600 | 3,500 | 2,500 | 7,500 |
| Neutrophil polymorphs. per cent. | 78 | 62 | 62 | 64 | 65 | 57 | 80 | 69 | 66 | 74 | — |
| Eosinophil polymorphs. per cent. | 1 | 1 | 2 | 1 | 2 | 1 | 2 | 3 | 5 | 1 | — |
| Basophil cells per cent. | 1 | 1 | 0 | 3 | 1 | 2 | 0 | 1 | 0 | 2 | — |
| Lymphocytes per cent. | 10 | 32 | 34 | 27 | 25 | 28 | 11 | 18 | 24 | 19 | — |
| Monocytes per cent. | 9 | 4 | 2 | 5 | 7 | 12 | 7 | 9 | 5 | 4 | — |
| Anisocytosis | Slight | Moderate | — | — | — | — | Marked | — | — | — | — |
| Poikilocytosis | Slight | Moderate | — | — | — | — | Marked | — | — | — | — |
| Platelets | — | 180,000 | — | — | — | 168,000 | — | 210,000 | 225,000 | 142,000 | — |
| Reticulocytes per cent. of R. B. C. | 40 | 50 | 60 | 20 | 20 | 30 | 15 | 20 | 12 | 15 | 4 |
| Normoblasts | 130 | 162 | 100 | 30 | 246 | 0 | 40 | 0 | 0 | 25 | 100 |
| Punctate basophilia | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Percent. of R. B. C. | Indirect positive 3-14 mg. % bilirubin | — | — | — | Indirect positive 1.5 mg. % bilirubin | — | — | — | — | — | — |
| Van den Bergh reaction | — | — | — | — | — | — | — | — | — | — | — |
| Fragility of R. B. C. | — | Increased | — | Increased | — | — | Increased | — | — | — | — |

but no red cells, blood-pigment, pus, casts, or bilirubin were found; the amount of urobilin was increased. A constant finding was an abundant, yellow, amorphous deposit, which gave the Prussian-blue reaction for iron. This was not more marked during the night than in the day. The Wasserman reaction was negative, but the Kahn test was strongly positive on three occasions. The first blood examination showed a macrocytic anaemia, with signs of irritation of the bone-marrow (Table II). A Price-Jones' curve

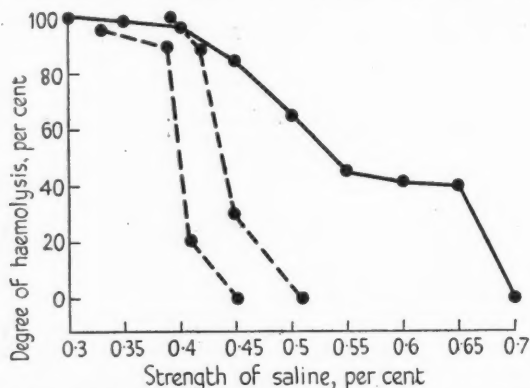


Fig. 3. Case 2 (Marchiafava-Micheli syndrome). Quantitative fragility curve (Whitby and Hynes's modification of Simmel's method).

————— = Degree of haemolysis of patient's red blood-cells.
 - - - - - = Degree of haemolysis of normal red blood-cells.

(Fig. 2) showed an increased mean cell diameter. The mean cell volume and the mean corpuscular thickness were within normal limits. The fragility of the red cells was increased (Fig. 3). The blood contained 3.14 mg. per cent. of bilirubin. The colour of the blood-plasma varied from pink to light brown, and spectroscopic examination showed bands corresponding to those of methaemoglobin.² The sedimentation-rate (Westergren's method) was increased. Chemical examinations of the blood gave the following results: blood-urea 24 mg. per cent., serum-calcium 8.95 to 11.2 mg. per cent., inorganic plasma-phosphorus 3.1 to 4.9 mg. per cent., plasma-phosphatase 1.34 mg. of phosphorus, plasma-chloride 361 to 393 mg. per cent., blood-cholesterol 53 to 80 mg. per cent. A possible explanation of the low cholesterol in the blood may be that owing to the destruction of the erythrocytes there was much wastage of their envelopes, which are rich in cholesterol. There was no further haemoglobinuria until the following May, when the urine contained oxyhaemoglobin, but no red cells. The haemoglobinuria was certainly not more marked during the night.

Further investigations. Further examinations of the blood were made, in an endeavour to confirm and establish some of the conditions under which haemolysis occurs *in vitro* in this syndrome. Venous blood was collected from the patient with maximal and minimal constriction of the vessels. The plasma and red cells were obtained by adding a small amount of heparin to samples of the blood and centrifuging at 2,000 revolutions per min. for 10 minutes at room temperature. The serum was obtained by allowing samples of venous blood to coagulate. The cells were washed with 0.9 per cent. saline, or with a buffer solution, and a 5 per cent. suspension

² Or methaemalbumin (Fairley, 1939).

of red cells was made. The complement used was fresh guinea-pig serum. All specimens were examined on the day of collection. The blood of healthy persons of the same blood-group as the patient was used for the control experiments. The following experiments with controls were repeated several times:

Exp. 1. The effect of temperature on haemolysis of the patient's whole and heparinized blood.

Venous blood from the patient was collected into eight tubes. In four it was allowed to clot; heparin had been added to the remainder.

| | 0° C. 1 hr. | 20° C. 1 hr. | 37° C. 1 hr. | 0° C. for 15 min. and 37° C. for 1 hr. |
|--------------------------|----------------|-----------------|-----------------|---|
| Whole blood: lysis | + | ++ | ++ | ++ |
| Heparinized blood: lysis | + | ++ | ++ | ++ |

These results are quite different from those of Donath and Landsteiner (1902), who found that in paroxysmal cold haemoglobinuria the blood had to be cooled and then heated to 37° C. for autohaemolysis to take place.

Exp. 2. The effect of oxygen and carbon dioxide on the haemolysis of the patient's whole and heparinized blood at different temperatures.

Blood was collected, with maximal constriction of the veins, into a series of test-tubes with and without heparin. In the first set the blood was collected in air. In the second under paraffin to prevent or retard the loss of carbon dioxide. In the third the blood was saturated with oxygen. The tubes were kept at 0° C., 20° C., and 37° C. for one hour; also, at 0° C. for seven minutes and then at 37° C. for one hour. In every tube lysis occurred, but it was minimal in those kept at 0° C. Ham (1937) found that when carbon dioxide was added to heparinized blood from a patient suffering from this syndrome, so that the partial pressure ranged from 4 to 40 mg. of Hg, immediate haemolysis occurred, the amount of which was proportional to the tension of the gas; but on equilibration with air or oxygen haemolysis did not take place. If the patient's red cells were washed and resuspended in his own plasma or serum, equilibration with carbon dioxide or the addition of lactic acid did not modify haemolysis. The addition of sodium bicarbonate, however, caused a decrease. Van den Bergh (1911) observed autohaemolysis at 37° C., but only in an atmosphere of carbon dioxide. Dacie, Israëls, and Wilkinson (1938), in a similar case, found that lysis did not take place if the sample of blood had been aerated, but that the onset was determined by the 'venosity' of the blood. They observed, further, that the omission of a covering layer of paraffin sufficed to prevent noticeable lysis. Mackenzie (1929) found that in paroxysmal cold haemoglobinuria carbon dioxide played no part in the production of haemolysis.

Exp. 3. The effect of temperature on haemolysis of a resuspension of the patient's washed cells in his own serum or plasma, which were separated at 0° C. and at 37° C.

Samples of whole blood from the patient and from a control were separated in an ice-chest and in the incubator at 37° C. The red cells were washed with pH 7.4 buffer solution (Sørensen).

Similar results were obtained by using plasma instead of serum. From these experiments, which support the views of Ham (1937), and Dacie, Israëls, and Wilkinson (1938), the essential abnormality in the Marchiafava-Micheli syndrome appears to be in the patient's red cells themselves and

not in the plasma. But since haemolysis does not take place if the patient's red cells are suspended in normal saline, there must be another factor essential for haemolysis, which is common to the plasma and serum both of the

| | At 20° C. for 1 hr. | At 37° C. for 1 hr. |
|---|------------------------|------------------------|
| | Haemolysis. | Haemolysis. |
| Patient's cells resuspended in patient's serum | + | + |
| Control cells suspended in patient's serum | 0 | 0 |
| Patient's cells suspended in control serum | + | + |
| Control cells resuspended in control serum | 0 | 0 |
| Patient's cells suspended in 0.9 per cent. saline | 0 | 0 |
| Control cells suspended in 0.9 per cent. saline | 0 | 0 |

patient and of the control. Dacie, Israëls, and Wilkinson (1938) have found that with a suspension of washed red cells in buffered plasma (pH 7.1), of a patient suffering from this syndrome, maximal lysis is obtained when the cell suspension is first cooled below 5° C. for fifteen minutes and then warmed to 37° C. for two to three hours, but when whole blood is used, preliminary cooling is unnecessary. From our experiments, we find that the same degree of lysis takes place in each case. We have found also, as they have, that when the patient's red cells are resuspended in his plasma, there seems to be an inverse relationship between the ease with which *in vitro* auto-haemolysis can be demonstrated, and the severity of the *in vivo* haemolysis.

Exp. 4. *The effect of heated serum on haemolysis of the red cells of the patient.*

Dacie, Israëls, and Wilkinson (1938), Ham (1937), and we ourselves have found that the lysis is thermolabile, for, after heating the patient's serum to 56° C. for half an hour and adding complement, its haemolytic properties are destroyed. We have observed no inhibiting factor in heated serum, since the addition of fresh unheated serum of the patient or of a control to the suspension of the patient's red cells in serum which had been heated to 56° C. caused lysis.

Exp. 5. *The effect of anticoagulants on haemolysis of the patient's red cells.*

We found that sodium citrate and potassium oxalate prevented haemolysis. Ham (1937) observed that normal serum haemolysed red cells which had been collected into citrate or oxalate and then washed. We could not confirm this observation.

Exp. 6. *Quantitative estimation of fragility.* (Whitby and Hynes's (1935) modification of Simmel's method.) Fig. 3.

The cells destroyed were estimated by counting the remaining cells.

| Saline per cent. | 0.35 | 0.4 | 0.45 | 0.5 | 0.55 | 0.6 | 0.65 | 0.7 |
|-------------------------------|------|------|------|-----|------|-----|------|-----|
| Percentage of cells destroyed | 98.6 | 97.4 | 85 | 66 | 46 | 42 | 40 | 0 |

Further progress and treatment. Iron in large doses and daily injections of a potent preparation of liver extract were given for some time. In view of the positive Kahn reaction, intensive courses of intramuscular injections of bismuth, and iodides by the mouth, were given, but no improvement occurred.

Ham (1937) noticed that in his case oral administration of alkalis caused a decrease in the intravascular haemolysis, and that withdrawal was followed

by a striking and prolonged increase in the haemoglobinuria. Dacie, Israëls, and Wilkinson (1938) found that if the pH of the blood *in vitro* was increased within physiological limits, haemolysis did not occur; so they suggested that large amounts of alkalis might be beneficial. These were given to our patient regularly for some weeks, but with no clinical or haematological improvement.

There seems to be no theoretical reason why the removal of the spleen should be of benefit in this disease, as there is no evidence that the reticulo-endothelial system is responsible for the increased blood destruction. Yet splenectomy has been performed in eight cases, four of which died shortly afterwards, but in two cases improvement occurred (Ham, 1937; Dacie, Israëls, and Wilkinson, 1938; Wilkinson, 1938). Therefore, since our patient was showing no signs of improvement and a fatal result seemed inevitable, Mr. Gerard Dyke agreed to remove the spleen. On the preceding day a slow drip transfusion was given, from a donor of the same group, after careful cross-matching. Next morning, the patient complained of a slight feeling of malaise and there was some coryza. An examination of the blood showed, for the first time, practically no reticulocytes. For the operation the anaesthetic used was gas, oxygen, and ether. Unfortunately, about half-way through the operation, generalized convulsions occurred, and the patient's temperature rose to 106° F. The anaesthetic was discontinued and evipan injected. The convulsions ceased and the operation was completed hurriedly, but he died shortly afterwards.

Looking back, it might have been better had the operation been postponed. The history of haemoglobinuria following a former injection of protein, the feeling of malaise and slight coryza on the morning of the operation, and the reduction in the number of reticulocytes, all pointed to the possibility of a reaction in spite of strict examination of the bloods for compatibility. In haemolytic anaemia the first blood transfusion should not be given shortly before an operation, as there is no opportunity for ascertaining its full effect.

Post-mortem examination. The autopsy was made twenty hours after death. Only positive findings are given. Brain, 50 oz. The blood was clotted throughout the body, the clots being of post-mortem type, but platelet thrombi were present in the basilar artery. It is probable that they were formed shortly before death and were associated with the convulsions which occurred during the operation. Heart, 17 oz. The muscle was hypertrophied. The aortic valve was competent to a water test, but the three cusps were thickened and partially calcified. Aortitis was present close to the valve, suggesting a syphilitic lesion. The coronary vessels and abdominal aorta appeared normal. Liver, 72 oz. It was enlarged, soft, and pale yellow in colour. Sections from this organ did not stain well, on account of autolysis. The cut surface of the kidneys had a distinct rusty colour, though the pattern was clear. The capsule stripped readily. There was a diffuse increase in the collagen fibres (Plate 20, Fig. 6). There was an absence of inflammatory cells in this fibrous tissue, and the latter did not appear to harm the renal tubules in any way. The glomeruli appeared normal, except for slight thickening of Bowman's capsule. The convoluted tubules showed a heavy deposit of haemosiderin, scattered evenly throughout the cells, similar to the case reported by Scott, Robb-Smith, and Scowen (1938). The bladder contained about 4 oz. of urine which was deeply stained with haemoglobin. Spleen, 20 oz.; measurements, 7 × 4 × 2 in.; capsule normal. No accessory spleens were found. Cut surface, deep red. The Malpighian

bodies were not a prominent feature. Microscopically, the red pulp showed no evidence of erythrophagocytosis, and there was a complete absence of iron pigment. The sinusoids were moderately distended, and the littoral cells showed relatively few changes (Plate 20, Fig. 7). The Malpighian bodies (Plate 21, Fig. 8) numbered just over 1 per low-power field. The majority were collections of small lymphocytes only, but were arranged loosely and stained uniformly. In the large bodies (diameter up to 2 high-power fields $\times 358$, Plate 21, Fig. 8), the germinal centres were composed of cells with small nuclei and abundant eosinophilic cytoplasm. They resembled those in lymph glands affected with sarcoidosis. Exactly similar cells have been seen by us recently in a case of syphilitic lymphadenitis. The finding of cells of this character, together with a syphilitic aortic lesion and a persistently positive Kahn reaction, suggests that there may have been an underlying syphilitic basis in this case for the whole syndrome, although spirochaetes were not found in the spleen. We have compared this spleen with those from three other cases of the Marchiafava-Micheli syndrome. There are material differences between them (Lescher and Osborn, 1939). The bone-marrow, generally, was deep red and hyperplastic. Cells of the red series predominated, macronormoblasts being the most numerous of the nucleated forms. Leucocytes and their precursors were relatively scanty, those present being of normal type. Megakaryocytes were numerous. There were also striking numbers of large phagocytic cells which had ingested up to three or four red blood-cells. These were more numerous in the bone-marrow than in other parts of the reticulo-endothelial system. The structure of the blood-clots was mainly post-mortem in type. The red cells showed a free mixture of normal forms with 'ghosts' (Plate 21, Fig. 9). Their presence afforded direct evidence of intravascular haemolysis. Unfortunately, no attempt was made to demonstrate them in the blood during life.

Discussion of Case 2. Ham (1937), Dacie, Israëls, and Wilkinson (1938), and we ourselves have found that in the Marchiafava-Micheli syndrome, also, the abnormality is in the red cell. Dameshek and Schwartz (1938 *a, b*), while agreeing, consider, further, that these cells have been sensitized by haemolysins in the plasma. Josephs (1938) is of the opinion that haemolysis is due to the diminution of a substance which appears to have some specific influence in reducing blood destruction, and which, usually, is present in normal plasma.

The haemolysins which can be demonstrated in different types of haemolytic anaemia vary considerably. The ones which are most familiar are those present in the plasma; they act on the erythrocytes in the presence of complement, and can be produced experimentally by injecting guinea-pig red cells into rabbits. The isohaemolysins of syphilitic paroxysmal haemoglobinuria are of a similar type. The haemolysin is present in the plasma and unites with the red cells in the presence of complement when the blood is chilled. Such plasma will attack the erythrocytes of a person of a similar blood-group, but there is no lysis of the cells themselves by a control serum of the same group. Haemolysins have been reported also in haemolytic anaemias thought to be non-syphilitic, and in typical acholuric jaundice. Dameshek and Schwartz (1938 *a*) have found isohaemolysins of the immune-body type in the sera of three cases of acute haemolytic

anaemia, which haemolysed red cells of their own group as well as those of group O. The sera possessed all the immunological properties of anti-guinea-pig serum. These authors have also found that by varying the dosage of injections of anti-guinea-pig serum into guinea-pigs, different types of the haemolytic syndrome can be produced at will. Thus, with 0.5 to 2.0 c.c. of anti-guinea-pig serum, a fulminating type of haemolytic anaemia followed in almost every case. The anaemia was microcytic, with nearly 100 per cent. of spherocytes, and the fragility of the red cells was greatly increased. There was but little evidence of bone-marrow regeneration. If the dose of haemolytic serum was only 0.2 c.c. daily, an acute haemolytic anaemia developed in most of the animals. The outstanding haematological feature was the development of spherocytes associated with a marked increase in erythrocytic fragility. Shortly afterwards, reticulocytes and nucleated red cells appeared. The animals either made an uneventful recovery or died. If the amount of haemolytic serum was small, i.e. 0.1 c.c. daily, a subacute anaemia occurred. The red cells were normal in size, and numerous reticulocytes, but no spherocytes, were seen. Usually, complete recovery took place. Therefore, Dameshek and Schwartz (1938c) believe that the various changes in the blood in haemolytic anaemias are due to haemolysins, possibly of different types, present in varying amounts, and modified by the individual's power to react.

The 'haemolysin' demonstrated in Case 2 is, however, very different from these simple haemolysins. Since it cannot be demonstrated in the plasma, it is doubtful whether it ought to be described as a 'haemolysin'. The abnormality is in the red cell itself, and haemolysis takes place just as readily with a control serum of the same group as it does with the patient's serum. As it is necessary to have serum, complement, and abnormal red cells for this reaction, it is customary to regard the haemolysis as the result of a haemolysin, though clearly this assumed 'haemolysin' is a normal serological substance acting on hypersensitive red cells. An attempt has been made to bring this into line with the more familiar haemolysins, by assuming that the red cells are sensitized by adsorbing the haemolysin from the plasma *in vivo* (Dameshek and Schwartz, 1938a, b). If this were so, the addition of heated serum plus complement, or of complement alone, should cause haemolysis. This did not occur in Case 2.

Unlike most of the reported cases of the Marchiafava-Micheli syndrome, the haemoglobinuria in our case was not essentially nocturnal. Corresponding to this, we found that *in vitro* haemolysis was independent of the state of oxygenation of the blood. This is quite different from the observations of Ham (1937) and those of Dacie, Israëls, and Wilkinson (1938), who found that the lysins present in the sera of their cases of this syndrome were extremely sensitive to slight changes in the hydrogen-ion concentration, and that increasing this within physiological limits encouraged haemolysis. In their cases haemoglobinuria was mainly nocturnal. They have suggested, as an explanation, that the rise in carbon-dioxide tension in the blood

during sleep leads to an increase of the hydrogen-ion concentration, with a resultant rise of haemoglobin in the plasma, above its threshold.

Thus, the haemolysins in different types of haemolytic anaemia vary widely in their properties. The conditions under which they can be demonstrated are very narrow in many cases. They should prove a fruitful field for further investigation, however, because in some instances it has been found relatively easy to inactivate them, e.g. by dietetic means (Rhoads and Miller, 1937), by normal serum (Dameshek and Schwartz, 1938*a*), or by giving a protein, fat-free substance, which Josephs (1938) claims to have isolated from the plasma of human beings and pigs, and to have found that it reduces or inhibits haemolysis in some cases of haemolytic anaemia.

In recent years research in blood diseases has been confined largely to the structure and functions of the red cell rather than of the serum. Further investigation is necessary into the presence and behaviour of haemolysins, and into the properties of the blood plasma in patients suffering from haemolytic anaemia.

Summary

1. A case of atypical (non-spherocytic) macrocytic jaundice and one of haemolytic anaemia with paroxysmal haemoglobinuria (approaching the Marchiafava-Micheli syndrome) have been reported and discussed. A description of the post-mortem examination of the latter case has been given.
2. Serological examinations of the blood of the case of the Marchiafava-Micheli syndrome have been made, in an endeavour to confirm and establish some of the conditions under which haemolysis takes place *in vitro* in this condition.
3. In both of the cases the abnormality was found to be in the red cells and not in the blood-plasma. The haemolysin in Case 2 differed from most other haemolysins, since it could not be demonstrated in the patient's plasma.
4. Further investigation is necessary into the presence and behaviour of haemolysins and the properties of blood-plasma in the various forms of haemolytic anaemia. In all cases the blood should be examined for the presence of 'ghost' cells, the plasma for blood-pigments, and the urine for haemosiderin.
5. The older classification of haemolytic anaemia into 'congenital' and 'acquired' groups is unsatisfactory. There are advantages in adopting the one suggested and used by Thompson (1936) and Whipple (1937).
6. There is some evidence that syphilis may have been a causal factor in the case of the Marchiafava-Micheli syndrome which has been described.

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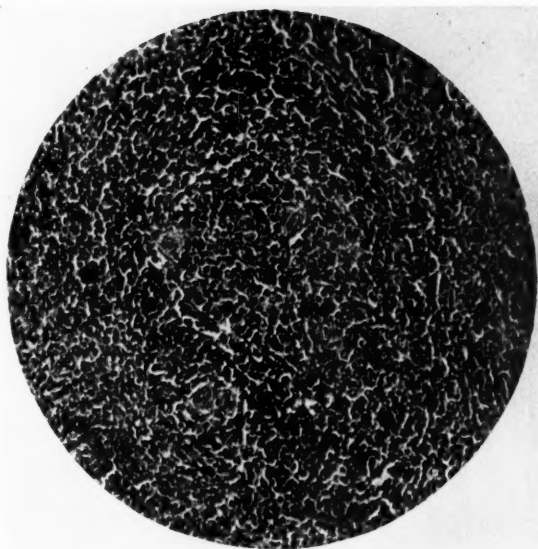


FIG. 4. Photomicrograph of Malpighian body from Case 1—*atypical (non-spherocytic) acholuric jaundice*. Note the 'germinal centre' composed of typical, large reticulo-endothelial cells and a peripheral zone of small lymphocytes. This is the same type of follicle as that seen in a lymph node, and in thrombocytopenic purpura

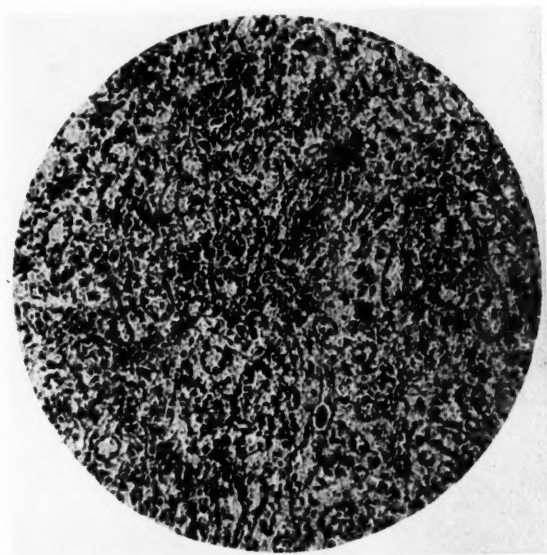


FIG. 5. Photomicrograph of splenic pulp from Case 1. Note the hyperplasia of the littoral cells

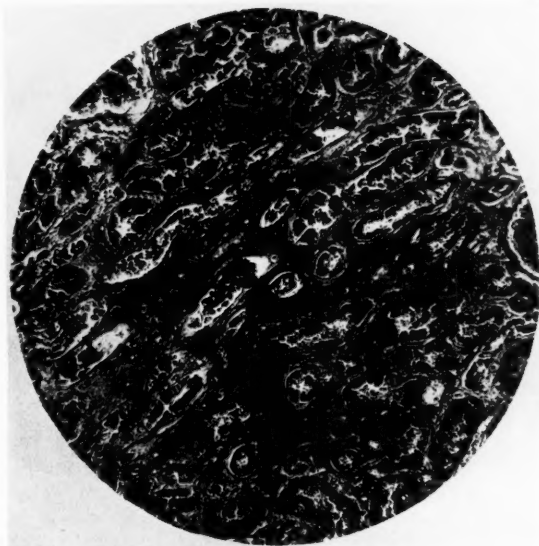


FIG. 6. Photomicrograph of kidney from Case 2—Marchiafava-Micheli syndrome—showing extensive fibrosis between tubules. Note the absence of inflammatory cells, and also the absence of damage to the tubules by the fibrous tissue (Masson's trichrome stain)

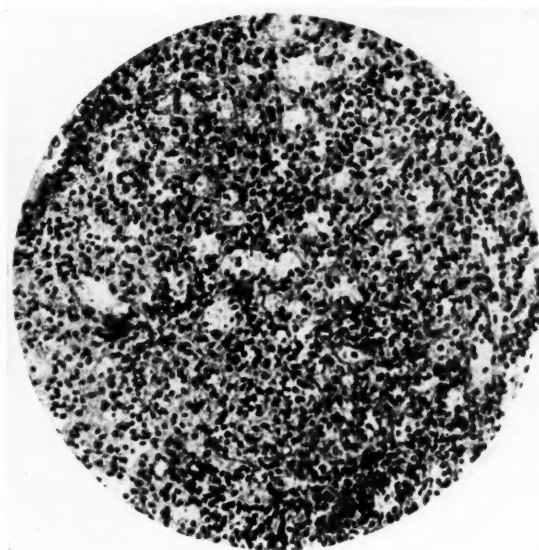


FIG. 7. Photomicrograph of splenic pulp from Case 2

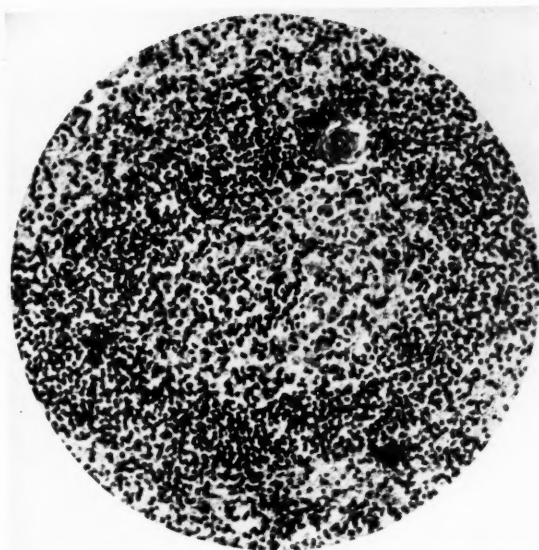


FIG. 8. Photomicrograph of Malpighian body from Case 2. Note the 'germinal centre' composed of small lymphocytes and large endothelial cells, with abundant pink-staining cytoplasm. The centre is pale compared with the peripheral ring of small lymphocytes

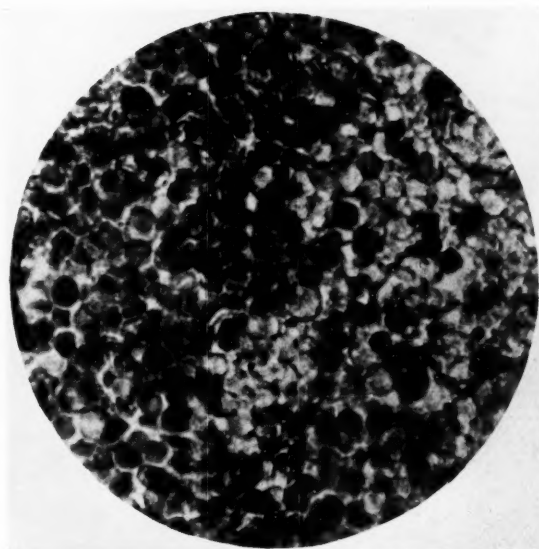
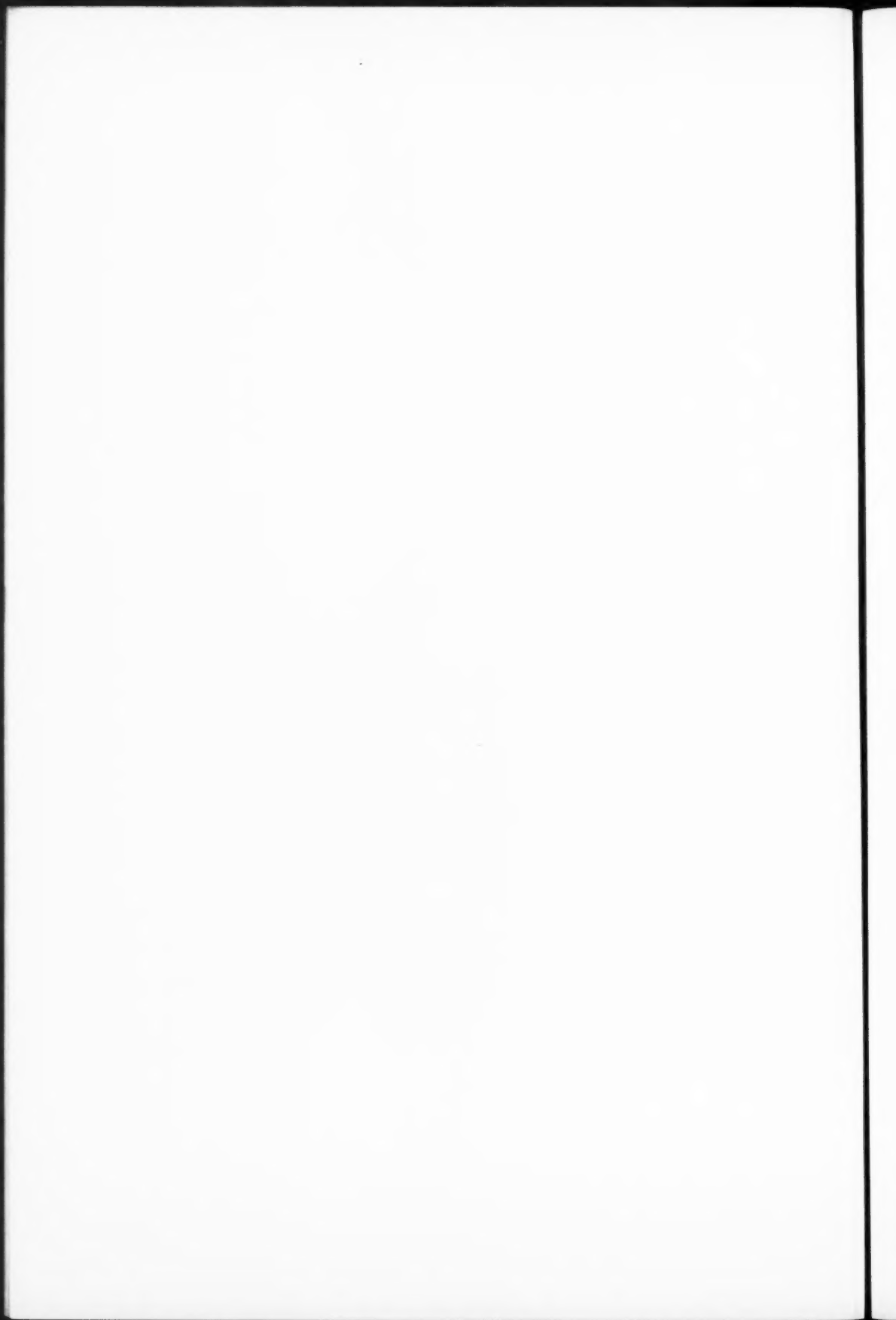


FIG. 9. Photomicrograph of blood-clot from abdominal aorta from Case 2. Note the contrast between pale 'ghost' cells and more normal red cells. Many of the 'ghost' cells are swollen (Haematoxylin and eosin)



THE NATURE OF THE ARTERIOLAR HYPERTONICITY IN ACUTE GLOMERULO-NEPHRITIS¹

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It may be taken as reasonably certain that the blood-pressure in the cardiovascular system is in general governed by Poiseuille's law of hydrodynamics:

$$P = \frac{8nlQ}{\pi R^4}.$$

P = pressure. Q = output of pump. n = coefficient of viscosity.
 R = radius (mean arteriolar radius). l = length.

R is influencing the pressure inversely in the fourth power. It is generally accepted that in the hypertension of disease the mechanism at work is excessive constriction of arterioles. This conclusion is based on the absence of conclusive evidence which incriminates any other factor in the equation. Pickering (1935) estimated the blood viscosity in four cases of acute glomerulo-nephritic hypertension during and after the hypertensive phase; he found no significant difference between the two sets of observations. The same worker also compared the arm to tongue circulation time during and after the hypertensive phase in a similar group of acute glomerulo-nephritics. Once again he found no significant difference and he concludes that 'it is unlikely that the raised pressure in acute nephritis is due to increased cardiac output'. A rather different conclusion was reached by Hayasaka (1927) who estimated the cardiac output in a series of hypertensive subjects, including one case of acute glomerulo-nephritis. He found an increased output in this single case. However, there are objections to the methods he employed. At the same time it is an observation that would bear repetition, using a more modern and more accurate method.

The mean arteriolar radius remains as the predominant factor in the control of arterial blood-pressure and, therefore, a search for the cause of hypertension must consist of the study of factors influencing peripheral vascular tone. The tonus of the arterioles is subject to two main sets of influences, (a) the nervous vasoconstrictor or extrinsic tonus, and (b) the inherent tonus of plain muscle or intrinsic tonus, and it will be seen from the accompanying diagrams that hypertension may, theoretically, be due to excess of either of those two factors. It must be emphasized that the relative value of these intrinsic and extrinsic factors varies in different areas

¹ Received June 14, 1939.

of the vascular territory, for instance, nervous influences are much greater in the skin blood-vessels of the hand than in muscle blood-vessels. Therefore, it is necessary in making deductions to compare the same area in different individuals or the same area in the same individual at different times. The distinction between 'extrinsic' and 'intrinsic' factors is to some extent artificial in view of the fact that vasomotor nervous impulses

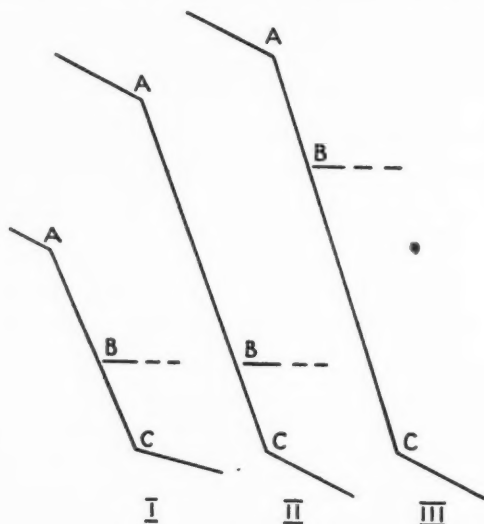


FIG. 1. AC represents the fall in blood-pressure that occurs in the arterioles, therefore AC is proportional to the degree of arteriolar tonicity.

AB represents the fraction of the arteriolar tissue which is mediated by vasomotor nerves.

BC represents the fraction mediated by non-nervous factors.

Curve I represents the normal, curves II and III demonstrate the possibility of excessive arteriolar tonicity (i.e. hypertension) being due to excess of either nervous or non-nervous influences.

exert their influence by the release of adrenaline or acetylcholine at nerve endings. If hypertension be due to an abnormal vasoconstriction arising through the action of the vasomotor nerves, then complete inhibition of vasomotor nervous impulses supplying a given territory should result in a greater blood-flow through this territory in the subject with hypertension than in the non-hypertensive subject. It is essential that the extent of the area thus deprived of its vasomotor influences should be small enough to avoid any substantial lowering of blood-pressure.

Pickering (1935) has estimated the blood-flow in the skin of the hand after inhibition of the nervous constrictor tonus by immersion of the other hand in water at 45° C. until the blood-flow is maximal and constant. The heat elimination of the hand was used as an index of blood-flow. He has thus studied the blood-flow in chronic hypertension and in acute glomerulonephritic hypertension. The results showed that, whereas the maximum blood-flow in chronic hypertension fell within normal limits, in acute

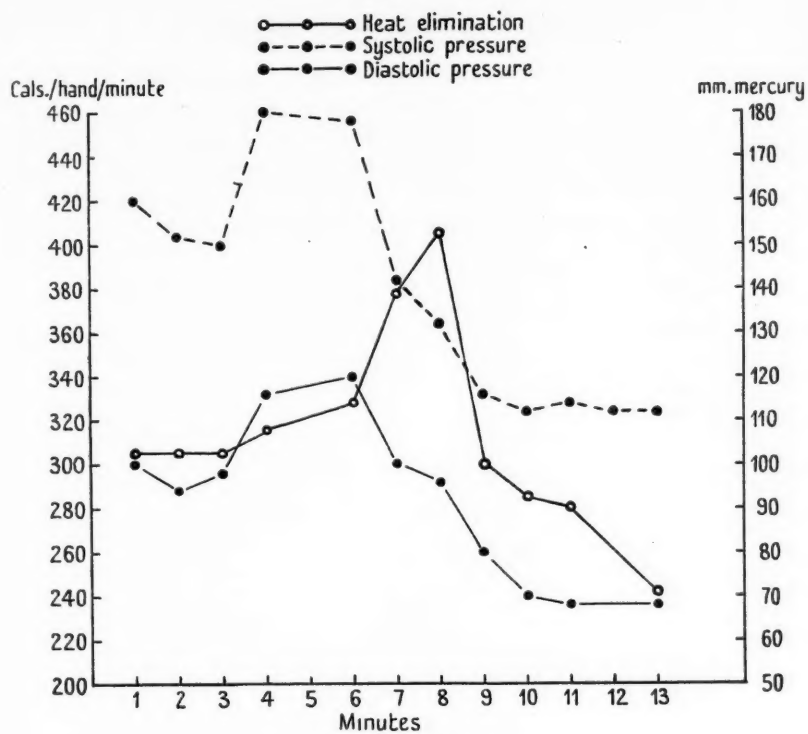


FIG. 2. Case 1.

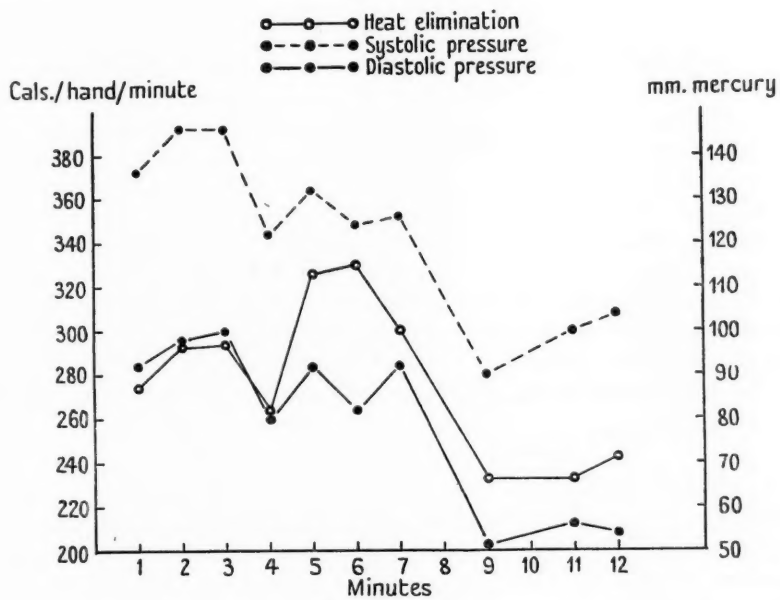


FIG. 3. Case 2.

hypertension, it was considerably greater during the hypertensive phase than during the subsequent phase of normal blood-pressure. In many respects the experiments on acute hypertension were more satisfactory in that comparison could be made between the normal and hypertensive phase in the same patient. We are in a position to confirm these observations with regard to acute nephritic hypertension. Prinzmetal and Wilson (1936)

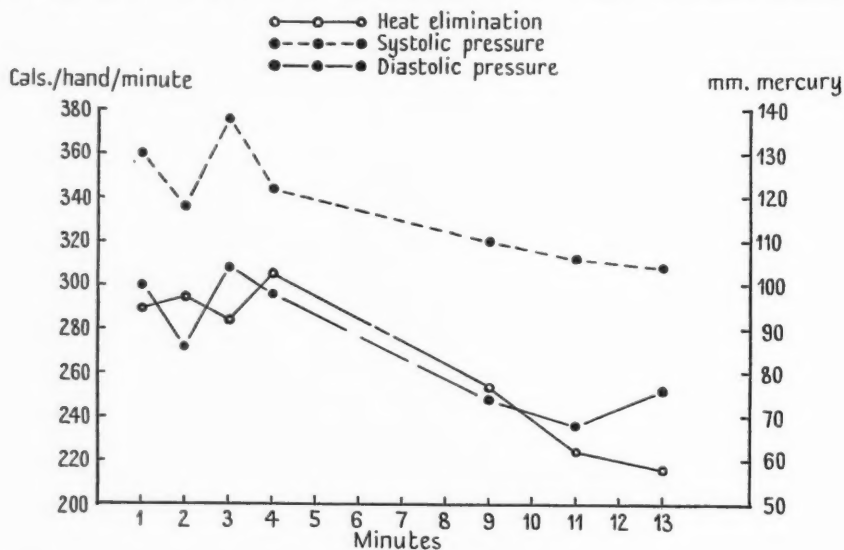


FIG. 4. Case 3.

carried out similar experiments in a variety of forms of hypertension including several cases of chronic hypertensive glomerulo-nephritis and one case of acute glomerulo-nephritic hypertension. They recorded forearm blood-flow with a modified Hewlett and Van Zwaluwenburg plethysmograph which indicates the increase in volume of a segment of forearm determined by the inflow of arterial blood, venous return having been abruptly obstructed by a cuff inflated to a venous occlusion pressure. They abolished nervous vasoconstrictor influences by novocaine injection of the stellate ganglion. They found that the increase in blood-flow obtained in both acute and chronic hypertensives was of the same order as in normal subjects. Their results, therefore, agree with those of Pickering (1935) in chronic renal hypertension, but differ sharply in the single case of acute renal hypertension.

Methods

A Stewart calorimeter fitted with an electrically driven mixer was used. Temperature was recorded to a hundredth of a degree Centigrade by means of a Beckmann thermometer with a magnifying eyepiece. The hand was immersed to the level of the distal carpal bones in the calorimeter filled with three litres of water at a temperature of about 30° C.; the other hand

was immersed in water at 45° C. After ten minutes, readings of calorimeter temperature were taken every minute until the rise each minute was maximal and constant. As the experiments had to be done in the open ward it was necessary to observe the cooling rate of the calorimeter after

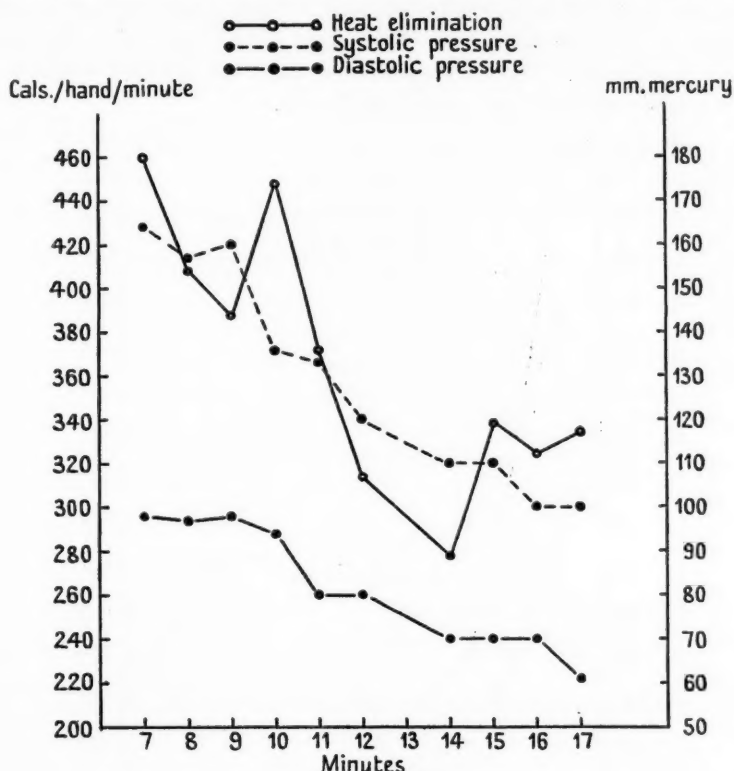


FIG. 5. Case 4.

each experiment and to add this figure to the rise per minute. The maximum heat elimination was calculated by multiplying the volume of water plus the heat equivalent of the calorimeter by the rise per minute plus the cooling per minute. The mouth temperature and blood-pressure were recorded before and after the experiment. As far as possible the experiments were repeated daily until the blood-pressure returned to normal.

| Case. | Age in years. | Maximum heat elimination per hand per minute, in calories. | |
|-------|---------------|--|-------------------------|
| | | Hypertensive phase. | Non-hypertensive phase. |
| 1 | 17 | 335 | 277 |
| 2 | 11 | 297 | 235 |
| 3 | 36 | 294 | 231 |
| 4 | 17 | 415 | 318 |
| 5 | 18 | 452 | 294 |

These results are expressed graphically in Figures 2 to 6.

Results

The blood-pressure was not substantially altered by the vasodilatation. It will be seen from the graphs and table that the maximum heat elimination was considerably higher during the hypertensive phase than during the subsequent period of normal blood-pressure. Cases 1 and 4 showed a curious elevation of the maximum heat elimination at the time when the blood-pressure was falling. We can suggest no explanation of this. Similarly we cannot explain the final high reading in Case 5.

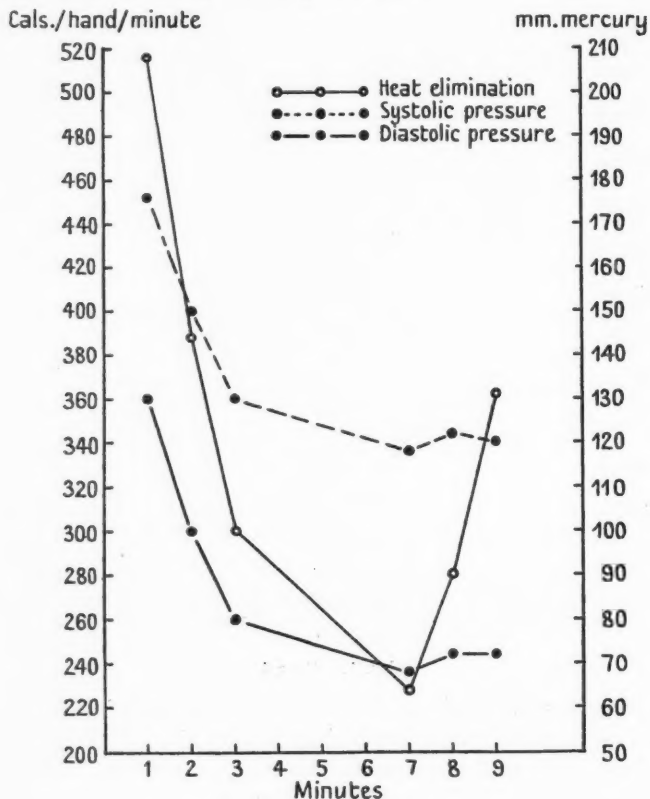


FIG. 6. Case 5.

Discussion

These observations confirm those of Pickering (1935), and they suggest that in the transitory hypertension of acute glomerulo-nephritis there is an abnormally high degree of nervous vasoconstrictor tonus. It is reasonable to conclude that such hypertonicity may be an important factor in the causation of the hypertension. The same method of investigation when applied to chronic hypertensive states (Pickering, 1935; Prinzmetal and Wilson, 1936) has shown no such enhancement of nervous vasoconstrictor

tonus. This confirms the hypothesis advanced by Pickering (1936) that there may be a difference in the mechanism causing arteriolar hypertonicity in acute renal and chronic renal hypertension. This possibility finds some experimental pathological support. We (Arnott, Kellar, and Matthew, 1936, 1937) have found that the development of the acute hypertension which occurs in rabbits following renal damage by sodium oxalate or by nephrotoxic serum appears to be dependent on the integrity of the renal nerve supply. On the other hand the chronic hypertension that occurs in dogs as the result of reduction of renal blood-flow is independent of renal nerves (Page, 1935; Collins, 1936; Goldblatt, 1937; Freeman and Page, 1937; Verney and Vogt, 1938). Indeed there is evidence that chronic renal hypertension may be due to an excessive production by the kidney of a vasoconstrictor substance.

In human hypertension various surgical methods of diminishing nervous vasoconstrictor influences have been tried and these have met with varying success (Martin, 1938). In a proportion of cases the results have been a prolonged depression of blood-pressure to normal or to near-normal levels; on the other hand many cases have shown no substantial lowering. This affords still further evidence that the arteriolar hypertonicity of renal hypertension in man is mediated partly by a nervous and partly by a non-nervous mechanism.

Conclusions

1. The maximum heat elimination from the hand in glomerulo-nephritic hypertension is greater in the hypertensive than in the non-hypertensive phase.
2. A dual nervous and non-nervous mechanism operates in human renal hypertension.

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We also wish to express our gratitude to Professor D. M. Dunlop and the other Physicians to the Royal Infirmary for their kind permission to investigate patients under their care.

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A STUDY OF SOME SERUM ELECTROLYTES IN HYPERTENSION¹

BY O. L. V. S. DE WESSELOW AND W. A. R. THOMSON

(From the Medical Unit, St. Thomas's Hospital)

With Plate 22

Introduction

THOUGH considerable progress has recently been made in the study of that type of hypertension which is produced by renal lesions, we are still entirely ignorant of the cause of 'essential' hypertension, the form of hypertension in which the renal function is, at first at all events, intact. Apart from renal lesions, persistent hypertension is found in association with certain endocrine disorders, and presumably results in some way from endocrine dysfunction; instances of such an association are the hypertension of the Cushing syndrome, the hypertension of the Achard Thiers syndrome, and the hypertension, at first paroxysmal and later persistent, of the adrenal paraganglioma. In all of these conditions the suprarenal gland—cortex or medulla—is involved, and there is a school of thought, of which the most prominent exponent is Goldzieher (1929), which believes that hypertension is the result of dysfunction of the adrenal cortex. In view of the known effects of extracts of the adrenal cortex and of epinephrine upon the electrolytes of the blood, it would seem that further study of the electrolyte content of the blood in essential hypertension might be of interest, especially as relatively little work has been done on the subject.

Ambard and Beaujard (1904) were among the first to claim that in Bright's disease retention of chloride was accompanied by a rise in blood-pressure, which was unaffected by the protein content of the diet. In 1922 Allen and Sherrill stated that they were able to effect a considerable reduction of the blood-pressure in severe hypertension by rigid restriction of the sodium chloride content of the diet. They did not differentiate the effect of sodium restriction from that of the chloride. These findings were subsequently contradicted by O'Hare and Walker (1923), while Mosenthal and Short (1923) could find no evidence that the sodium chloride of the whole blood was increased in hypertension, and in hypertension without renal deficiency found that 10 gm. of sodium chloride by mouth produced no effect upon the blood-pressure within two hours. Berger and Fineberg (1929), giving amounts of sodium chloride up to 30 gm. daily to patients with essential hypertension, were unable to find any modification of the blood-pressure curve which could be definitely attributed to variations of the sodium-chloride intake. McQuarrie, Thompson,

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and Anderson (1936), by giving sodium chloride, raised the systolic blood-pressure of young diabetics with normal blood-pressure by 40 to 50 mm. of Hg. and the diastolic pressure to a corresponding degree, at the same time reducing the glycosuria. The effect of sodium bicarbonate and sodium citrate was similar but less striking.

Kylin (1937) found in essential hypertension a raised serum-potassium and a slight hypocalcaemia, as did Brems (1926) and Loewenstein (1928). According to Kylin, the potassium is about 5 mg. per 100 c.c. above the normal, and the calcium 0.6 mg. per 100 c.c. below the normal, and he states that the serum-sodium is frequently raised above the normal figure in essential hypertension, but his figures show no direct relationship between the height of the blood-pressure and the level of the serum-sodium.

Our work was planned firstly to include the examination of the sodium, potassium, and calcium of the serum in a group of patients with hypertension and a group of normal subjects, both groups having been kept on a ward diet for one week before investigation; secondly to determine the effects, if any, of artificially produced changes of the serum-sodium and potassium upon the hypertension.

Methods

Blood was withdrawn at noon, the patient having had no food or drink after the ward breakfast which is finished at 8.30 a.m. Serum used for the sodium, potassium, and calcium determinations was separated within one and a half hours after withdrawal of blood. Samples showing haemolysis were discarded, and all estimations were performed in duplicate. Serum-sodium was determined by the method of Butler and Tuthill (1931), potassium by the method of Kramer and Tisdall (1921*a*) as modified by Peters and Van Slyke (1932), and calcium by the method of Kramer and Tisdall (1921*b*) as modified by Clark and Collip (1925).

The ward diet, exclusive of added salt, consists approximately of protein 70 gm., carbohydrate 200 gm., fat 90 gm., sodium 1.3 gm., potassium 2.2 gm.; the total intake of sodium is probably somewhat low owing to paucity of added sodium chloride, the potassium content being nearer the generally accepted normal. Thus in our 20 normal, non-hypertensive patients the twenty-four hours urinary excretion of sodium was 2.3 gm., the average excretion on an ordinary diet, according to Peters and Van Slyke (1932), being 3 to 6 gm., mainly derived from added salt, while the daily urinary excretion of potassium was 2.0 gm., as against the normal figure of 2 to 4 gm.

During the long-term experiments patients were kept at rest in bed. Blood-pressure readings were taken at noon with a mercury sphygmomanometer, the patient having been kept behind screens for the preceding thirty minutes; in every case four readings were taken and the average of these accepted as representing the true pressure. No medication was employed, other than theominal in a few patients who suffered from severe headaches, and, if given, it was continued throughout the whole experiment.

Clinical Material

With the exception of one case of malignant hypertension, our cases of hypertension were unselected and taken as admitted. Mild cases of hypertension in which the diastolic pressure fell below 100 mm. of Hg after a week's rest in bed were excluded. Although traces of albumin were present in the urine of the majority, in 25 out of 36 cases the blood-urea was below 40 mg. per 100 c.c., so that no severe renal damage can have been present; of the remainder five had a blood-urea below 50 mg. per 100 c.c., the maximum figure obtained being 106 mg. per 100 c.c. in a case of malignant hypertension. Three patients suffering from malignant hypertension and one patient with essential hypertension, who developed a cerebral haemorrhage, died while in hospital. The largest age group (12 cases) was in the decade 40 to 50 years; three cases were below the age of 40, and three were over 70. Five cases may be classified as malignant hypertension, and of these four are now dead; the remainder may fairly be regarded as cases of essential hypertension of moderate severity. In no case was there a history of preceding nephritis.

The serum cations in normal and hypertensive subjects. The distribution of serum-sodium, potassium, and calcium, as estimated after the patients had been for one week on a ward diet, is shown in Fig. 1. In view of the fact that the normal individual under our conditions shows extremely constant figures, sodium was estimated in only 20 cases, an additional 10 normal subjects being investigated in the case of potassium and calcium on account of the wider variations met with in the case of the former.

Normal subjects. Serum-sodium. Among recent figures from the literature, the following may be taken as representative of the normal findings:

Hald (1933), 10 cases; range 297 to 330 mg. per 100 c.c., average 310.

McCance (1937), 5 cases; range 317 to 357 mg. per 100 c.c., average 335.

Maizels (1936), 6 cases; range 313 to 327 mg. per 100 c.c., average 320. Our own normal subjects, investigated under relatively constant dietary conditions, show a smaller range, 320 to 329 mg. per 100 c.c., average 323. As already pointed out, it is probable that the ward diet was somewhat low in sodium, on account of paucity of added salt.

Serum-potassium. A large series of estimations of the normal serum-potassium is available in the literature and without exception show a relatively wide range. As representative figures we may give:

Hald and Eisenman (1937), 16 cases; range 13.2 to 25.3 mg. per 100 c.c., average 17.7.

McCance (1937), 5 cases; range 13.2 to 19.9 mg. per 100 c.c., average 17.2.

Scudder, Smith, and Drew (1939), 60 cases; range 13.5 to 21.5 mg. per 100 c.c., average 17.2.

The methods employed by these workers were respectively the chloroplatinate, the cobaltinitrite method of Kramer and Tisdall, and the silver

cobaltinitrite method using heparinized blood. Though the cobaltinitrite method has been the object of much criticism, mainly owing to the difficulty of obtaining a precipitate of constant composition, it would seem that it yields results comparable to those obtained by other methods, and that it gives figures for the potassium content of normal human serum which are practically the same as those obtained by the classical macrogravimetric methods. Our

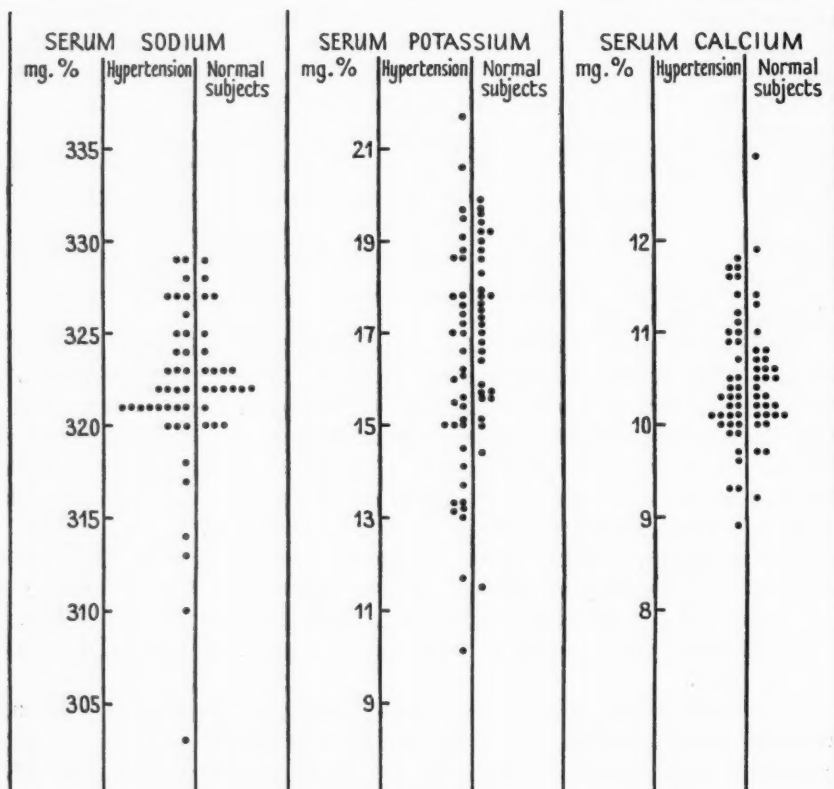


FIG. 1.

duplicate determinations corresponded closely, and the possibility of seepage of potassium from the potassium-rich corpuscles was guarded against by removal of the serum from the clot as early as possible. Our own 30 normal subjects show an extreme range of 11.5 to 19.9 mg. per 100 c.c., average 17.2. With the exception of one female patient, complaining of unexplained abdominal pain without vomiting, in whom the abnormally low figure of 11.5 mg. per 100 c.c. was found, our figures fall within the generally accepted range, and are all above 14 mg. per 100 c.c.

Serum-calcium. Our normal figures call for no remark.

Hypertensive subjects. There appears a definite tendency towards a low serum-potassium in the hypertensive. While of 30 controls only three showed

a serum-potassium of 15 mg. or under, the serum-potassium in 13 of 36 hypertensive patients was at or below this figure. A closer inspection of the group of hypertensive subjects in whom the lowest serum-potassium figures

TABLE I
The Findings in Patients with Malignant Hypertension

| Case No. | Date. | Blood-urea. mg. % | Serum. | | Urine. | | Remarks. |
|----------|----------|----------------------|------------------|------------|-------------------|------------|---|
| | | | Sodium. | Potassium. | Sodium. | Potassium. | |
| | | | mg. per 100 c.c. | | gm. per 24 hours. | | |
| 1 | 26.2.39 | 16 | 310 | 10.1 | 2.0 | 1.9 | Vomited once in preceding week. |
| | 3.3.39 | 22 | 310 | 11.8 | 2.0 | 6.0 | Pot. cit. 15 gm. daily for preceding 7 days. |
| | 8.3.39 | 33 | 306 | 22.8 | | | Pot. cit. 15 gm. daily and pot. chlor. 15 gm. daily for preceding 5 days. Much vomiting, and convulsions. |
| | 20.3.39 | 20 | 307 | 7.5 | 0.9 | 0.7 | No vomiting. |
| | 4.4.39 | 20 | 306 | 11.4 | Trace | 0.5 | No vomiting for 5 days. |
| 2 | 21.1.38 | 88 | 318 | 13.4 | 2.7 | 1.2 | No vomiting for 5 days. |
| | 28.1.38 | 93 | 316 | 15.1 | 0.9 | 1.0 | Low sodium diet for preceding week. No vomiting. |
| | 4.2.38 | 103 | 306 | 22.2 | 0.3 | 2.0 | Low sodium diet + pot. cit. 15 gm. daily for preceding 5 days. No vomiting. |
| | 11.2.38 | 89 | 310 | 13.3 | 1.5 | 1.5 | Ward diet. No vomiting. |
| | 22.2.38 | 82 | 306 | 10.5 | 1.6 | 0.6 | Ward diet. No vomiting. |
| 3 | 27.10.37 | 29 | 321 | 11.6 | 0.2 | 1.8 | Vomiting. |
| | 5.11.37 | 67 | 310 | 18.9 | | | Low salt diet for 7 days + 54 gm. pot. cit. in this period. Some vomiting. |
| | | | | | | | No vomiting for 2 days. Vomiting previously. |
| 4 | 18.4.39 | 106 | 303 | 13.3 | 1.6 | 2.9 | No vomiting. |
| | 26.4.39 | 120 | 306 | 20.0 | | | No vomiting. |
| | 9.5.39 | 103 | 319 | 18.1 | 6.4 | 4.6 | No vomiting. Improving. |
| 5 | 5.6.39 | 50 | 322 | 13.1 | 1.8 | 1.9 | No vomiting. |

occurred yields somewhat surprising results. Of eight hypertensive patients in whom at the first examination the serum-potassium was below 14 mg. per 100 c.c., five were of the malignant type, and of these four are since dead. These patients all showed papilloedema, agonising headaches, and high diastolic pressures; none of them showed cardiac oedema. No other cases of malignant hypertension were encountered in our series. Further details of these cases are given in Table I. In Case 1 a previous estimation at the National Hospital for Nervous Diseases had shown a serum-potassium of 8 mg. per 100 c.c. The other noticeable feature of these cases is a tendency to a definitely low serum-sodium level; three of them showed an initial serum-sodium below 320 mg. per 100 c.c., and there is a tendency to a persistently low level.

The reason for these low potassium and sodium figures is altogether obscure. The low potassium certainly bears no relationship to renal damage,

since in our experience chronic nephritis with nitrogenous retention shows either a normal or high serum-potassium, as was also found by Rabinowitch (1924). The possibility that the fall in these two cations may be the result of vomiting is not supported by our experience. The serum-potassium may remain at a low level without vomiting, and on a ward diet. The lowest figure in our series was met with in a patient who had not vomited for twelve days and who was taking her normal diet. The excretion of potassium with these low levels of serum-potassium tends to be low, and the serum-potassium can be restored to a normal figure by administration of potassium salts by mouth. Such a restoration is not, however, accompanied by any subjective or objective improvement in the patient's condition, but rather the reverse, and the serum-potassium soon falls to a low level when administration of potassium is discontinued.

The question arises whether the observed electrolyte changes in these patients were attributable to endocrine disturbances. Among hormones which lower the serum-potassium of the normal subject are insulin, adrenaline, and the adrenal cortical hormone. The adrenal cortical hormone lowers the serum-potassium level and promotes an increased excretion of potassium, of which there is no suggestion in our figures; it also produces sodium retention. Even if the sodium retention is masked by an accompanying hydraemia, the serum-sodium should be at least at a normal level. In our cases the serum-sodium tends to be low, and in some instances the excretion is at an approximately normal figure. Though adrenaline is known to lower the serum-potassium in man (Castleden, 1937; Allott and McArdle, 1938), it is stated by Keys (1938) to produce a small but significant increase in the serum-sodium. Insulin again, when given in massive doses to schizophrenic patients, produces a very appreciable fall in the serum-potassium, accompanied by a slight rise in the serum-sodium. The findings in our cases are therefore not consonant with the known action of any of these hormones.

It does not seem that the low serum-sodium which is frequently seen in these cases of malignant hypertension is due either to deficient intake or to vomiting; in normal and hypertensive subjects maintained for a week on a low salt diet we did not find that the serum-sodium fell below 315 mg. per 100 c.c., the excretion of sodium falling in some cases to as low a figure as 0.4 gm. in the twenty-four hours. On the other hand, there appears to be no question of excessive excretion of sodium, such as is seen in Addison's disease, in which we have seen such amounts as 5 gm. of sodium excreted daily when the serum-sodium was less than 300 mg. per 100 c.c. In our cases of malignant hypertension the excretion of sodium appears to be erratic and to have little relationship to the level of sodium in the serum. Apart from this small group of malignant hypertensive cases, the serum-sodium was below 320 mg. per 100 c.c. in only two cases (313, 317), in one of whom it subsequently returned to a normal level. The serum-calcium of the hypertensive group is approximately at a normal level, the only serum-calcium below 9 mg. per 100 c.c. being associated with nitrogenous retention.

The effect of sodium and potassium salts on the blood-pressure. In estimating the effect of any therapeutic procedure in the treatment of hypertension, the chief difficulty lies in excluding the influence of rest in bed and hospitalization on the blood-pressure, since, as is well known, a raised blood-pressure often falls to a lower level under these conditions without any other treatment. In our cases we have in the first place limited treatment to rest in bed for one week, the patient being on an ordinary ward diet; we have then tested the effect of the therapeutics, which we wished to study, for a week or longer, and have lastly placed the patient again on a ward diet for an after-period of one week as a control. Complete rest in bed has been our rule throughout, and no drugs other than an occasional purgative as required, have been administered; in a few cases theominal has been given twice daily, and in these it has been continued throughout the test and control periods.

The test periods are of necessity short, since the convenience of the patient and the pressure on hospital beds necessarily restrict the time over which such observations can be made. As a result there must be a certain overlap from period to period—for instance, a patient who has been taking a high salt diet will probably be unable to rid himself entirely of the additional salt for a day or two after the salt dosage has been discontinued—and as a result the changes in blood-pressure due to any particular form of treatment will tend to be minimized. Blood was taken for analysis on the last day of each period, and a twenty-four hour collection of urine made. An electrocardiogram was taken on the same day.

The effect of sodium citrate and sodium chloride on the blood-pressure. The response of the blood-pressure to sodium salts was studied in five patients, four female and one male. The results are shown in Table II. After one week on a ward diet, 15 gm. of sodium citrate was given daily for one week, followed by the same amount of this salt and an equal amount of sodium chloride for a further week, the patients then returning to a ward diet without any additional sodium salts for one week. In all cases a considerable rise occurred in the serum-sodium in the third week, and at the same time there was a tendency for the serum-potassium to fall. The serum-calcium was unaffected, and the pulse-rate remained unchanged. In every case the blood-pressure, both systolic and diastolic, showed a rise during the week in which the patients were receiving both sodium citrate and sodium chloride, and a definite fall in the succeeding week in which they returned to an ordinary ward diet. This rise was accompanied by a fall in the haemoglobin, which we accepted as evidence of blood dilution, and by a slight gain in weight, averaging about one pound. Of approximately 10 gm. of added sodium, about half was apparently being excreted in the urine at the end of the third period, and at the end of the after-period the sodium excretion was still above that of the fore-period.

We feel justified in concluding that an excess of sodium in the diet produces a slight but definite rise in the blood-pressure, both systolic and diastolic.

TABLE II

The Averages of the Findings in Five Patients with Hypertension to whom Sodium Salts were Administered

| Treatment. | Serum. | | | Blood- urea. | Hæmo- globin | Urine. | | Blood- pressure. |
|---|------------------|-------|----------|-----------------|-----------------|---------|------------|---------------------|
| | Sodium. | | Calcium. | | | Sodium. | Potassium. | |
| | mg. per 100 c.c. | mg. % | | | | | | |
| Ward diet (7 days) | 323 | 15.5 | 10.1 | 29 | 109 | 1.6 | 0.9 | 180/106 |
| Ward diet + sodium citrate (7 days) | 327 | 14.5 | 10.1 | 27 | 105 | 4.7 | 1.0 | 175/103 |
| Ward diet + sodium citrate + sodium chloride (7 days) | 333 | 13.5 | 10.7 | 25 | 95 | 7.2 | 1.0 | 186/108 |
| Ward diet (7 days) | 322 | 15.9 | 10.6 | 33 | 99 | 2.6 | 1.5 | 171/102 |

TABLE III

The Averages of the Findings in Three Patients with Hypertension, in whom an Attempt was made to Effect Sodium Depletion by Means of Sweating

| Treatment. | Serum. | | | Blood- urea. | Hæmo- globin. | Urine. | | Blood- pressure. | Weight. pounds. |
|--|---------|------------|----------|-----------------|------------------|---------|------------|---------------------|--------------------|
| | Sodium. | Potassium. | Calcium. | | | Sodium. | Potassium. | | |
| | | | | | | | | | |
| Ward diet (7 days) | 323 | 16.0 | 10.7 | 29 | 94 | 3.2 | 2.2 | 195/138 | 173 |
| Low sodium diet (7 days) | 324 | 16.2 | 10.3 | 32 | 95 | 0.5 | 0.8 | 179/133 | 171 |
| Low sodium diet + sweating (10 days) | 321 | 17.5 | 10.6 | 28 | 93 | 0.4 | 1.0 | 174/124 | 167 |
| Low sodium diet + sweating + 2 pints dis- tilled water daily (8 days) | 319 | 17.4 | 10.4 | 27 | 102 | 0.4 | 0.8 | 171/127 | 169 |
| Low sodium diet + sweating + 6 pints dis- tilled water daily (5 days) | 318 | 16.8 | 10.2 | 25 | 103 | 0.4 | 1.1 | 170/125 | 167 |
| Ward diet (7 days) | 323 | 18.1 | 10.4 | 29 | 93 | 3.7 | 2.6 | 171/117 | 172 |

Such rise as occurs is due to the sodium ion and not to the chloride ion, since, as will be seen later, potassium chloride has no such effect. It is possible that larger doses of sodium salts, or the same dose continued over longer periods, might produce more definite effects, but the actual amounts given were as much as the patients could easily tolerate and considerably exceeded any quantity which would occur in an ordinary, freely chosen diet.

As a corollary to these experiments we decided to investigate the effect of sodium depletion on the blood-pressure of hypertensive patients. Three such patients were first kept for one week on an ordinary ward diet; then for one week on a low sodium diet estimated to contain approximately 360 mg. of sodium per diem; then for ten days on the same low sodium diet with sweating in a hot-air bath at 120° F. for one hour daily. The sweating and low sodium diet were continued for another eight days and two pints of distilled water were added to the diet, making the total daily consumption of fluids four pints; for another five days the same regime was continued, the distilled water being increased to six pints daily. Finally they were put back on an ordinary ward diet with free consumption of fluids and without sweating for a week, as a control.

The results obtained are summarized in Table III. The most striking feature of the experiment is our failure to reduce appreciably the sodium concentration of the serum, in spite of the fact that the patients sweated freely and the average loss of weight amounted at its maximum to six pounds, with an approximate haemoconcentration of 10 per cent. as judged by the haemoglobin estimations. In similar but more drastic experiments by McCance (1936), much more marked falls in the serum-sodium were recorded, and greater degrees of haemoconcentration. It is to be noted that his patients suffered from anorexia, nausea, and cramps, symptoms which were not present in our cases. While in one of our patients the serum-sodium fell from 321 to 311 mg. per 100 c.c., in the other two the maximum fall amounted to only 5 and 7 mg. per 100 c.c. The serum-sodium was at its lowest when, in addition to a low sodium intake and sweating, large amounts of distilled water were being administered, and the haemoconcentration was also most marked under these conditions. The potassium and calcium of the serum were unaffected. The electrocardiogram was unaltered. In view of the haemoconcentration and loss of weight recorded, it is reasonable to assume that considerable depletion of the body sodium occurred, though no actual balance experiment was carried out. Samples of sweat contained approximately 50 mg. of sodium per 100 c.c., and during the actual hot-air bath 16 per cent. haemoconcentration with marked loss of weight occurred. The haemoglobin percentage given in Table III was estimated prior to the daily hot-air bath.

We were so much impressed with the difficulty of reducing the serum-sodium in our patients with hypertension by the methods adopted that we subjected a case of sciatica with normal blood-pressure to a similar course of treatment to determine whether the conservation of the serum-sodium was

in any way peculiar to the hypertensive subject. The figures obtained were practically identical.

The effect of sodium deprivation on the blood-pressure appears to have been negligible. During the after-period there was no rise in the systolic and a slight fall in the diastolic pressure, though the haemodilution and increase in weight suggest that the sodium content of the body had been fully restored, a suggestion which is supported by the resumption of a normal sodium excretion. Observations on the blood-pressure for a further six days after the end of the actual experiment confirm this conclusion. The progressive fall in blood-pressure which occurred in these cases during the experiment would therefore appear to have been due to rest in bed and hospitalization rather than to depletion of the body serum. In the normal case subjected to the same routine no change in blood-pressure occurred, a finding confirmatory of McCance's (1936) observations.

The effect of potassium citrate and potassium chloride on the blood-pressure. The effect of potassium salts was followed in two groups of patients. The first group (Table IV), four in number, after a control period were kept for one week on a diet low in sodium, and then received a daily addition of 15 gm. of potassium citrate to the low sodium diet, our aim being to alter the potassium:sodium ratio as far as possible. The second group (Table V), two patients, received a ward diet throughout, 15 gm. of potassium citrate being added during the second week of the experiment, and 15 gm. of potassium citrate and 15 gm. of potassium chloride during the third week.

As is well known, it is difficult to raise the potassium content of the serum to a high level, owing to the rapidity with which this ion is excreted by the kidneys, and, with one exception, the serum-potassium of our patients did not rise above 22.2 mg. per 100 c.c. In cases of gross renal deficiency, much higher levels may be reached. Thus in one case of chronic glomerulonephritis with gross nitrogenous retention we have seen a rise from 16.2 to 33.1 mg. per 100 c.c. on as small a dose as 5 gm. of potassium citrate daily for three days. In one case of this series, showing a malignant type of hypertension with urea retention (88 mg. per 100 c.c.) and a tendency to a low potassium and sodium level in the serum, a rise from 13.3 to 22.2 mg. per 100 c.c., with poor potassium excretion, occurred on the ingestion of potassium salts, and in another severe hypertensive without nitrogenous accumulation in the blood a figure of 25.2 mg. per 100 c.c. was attained, though in this patient more than the average urinary excretion of potassium was occurring. Both these patients had received potassium citrate alone, without potassium chloride, for seven days. Slight, irregular changes in the sodium level of the serum occurred, the mean figure for both groups being unaffected. Such alterations in the potassium:sodium ratio as occurred were therefore due almost entirely to the rise in the potassium. The administration of the potassium salts was accompanied by a loss of weight of 2 to 4 pounds and by evidence of slight haemoconcentration. The pulse-rate was unaffected.

TABLE IV

The Averages of the Findings in Four Patients with Hypertension, to whom Potassium Citrate was Administered

| Treatment. | Serum. | | Blood-urea. | Urine. | | Blood-pressure. |
|--|------------------|------------|-------------|-------------------|------------|-----------------|
| | Sodium. | Potassium. | | Sodium. | Potassium. | |
| | mg. per 100 c.c. | | mg. % | gm. per 24 hours. | | mm. Hg |
| Ward diet (7 days) | 319 | 17.4 | 47 | 2.7 | 1.9 | 217/131 |
| Low sodium diet (7 days) | 320 | 17.6 | 51 | 0.7 | 1.0 | 196/124 |
| Low sodium diet + potassium citrate (7 days) | 320 | 23.3 | 56 | 0.6 | 5.6 | 184/120 |
| Ward diet (7 days) | 321 | 17.8 | 50 | 2.6 | 2.2 | 191/120 |

TABLE V

The Averages of the Findings in Two Patients with Hypertension, to whom Potassium Salts were Administered

| Treatment. | Serum. | | Blood-urea. | Haemoglobin. | Urine. | | Blood-pressure. | Weight. |
|---|------------------|------------|-------------|--------------|-------------------|------------|-----------------|---------|
| | Sodium. | Potassium. | | | Sodium. | Potassium. | | |
| | mg. per 100 c.c. | | mg. % | per cent. | gm. per 24 hours. | | mm. Hg | pounds. |
| Ward diet (7 days) | 326 | 16.3 | 27 | 106 | 2.0 | 1.7 | 171/119 | 192.5 |
| Ward diet + potassium citrate (7 days) | 324 | 18.4 | 27 | 112 | 1.0 | 8.1 | 151/107 | 190 |
| Ward diet + potassium citrate + potassium chloride (7 days) | 322 | 21.3 | 26 | 109 | 1.4 | 15.3 | 134/98 | 190 |
| Ward diet (7 days) | 325 | 18.5 | 22 | 95 | 2.8 | 2.4 | 150/106 | 190 |

With potassium citrate alone the only effect upon the blood-pressure would appear to be a slight fall in the systolic pressure, the diastolic remaining unaffected. With higher potassium dosage, in the form of both citrate and chloride, a definite fall occurs in the systolic, with a less marked reduction of the diastolic pressure, resulting in a reduction of the pulse-pressure. These effects make it clear that the tendency to a rise in blood-pressure with the administration of sodium chloride is due to the sodium ion rather than the chloride ion.

Discussion

It would appear from the above findings that such changes as occur in the blood-pressure of hypertensive patients from the addition of amounts of potassium and sodium salts to the diet, which would be unlikely to be selected voluntarily by a patient, are relatively insignificant. Broadly speaking, the addition of considerable quantities of sodium to the diet in the form of the citrate and the chloride produces a rise in the blood-pressure of such patients, while the addition of the corresponding potassium salts produces a fall.

Assuming that the raised blood-pressure in essential hypertension is dependent upon a raised tonus of the peripheral vessels, it is questionable whether the changes observed are necessarily dependent upon a change in such tonus. Two other factors must be considered, changes in the blood-volume, and the possible effect of these two ions upon the heart.

With sodium dosage the estimations suggest that a definite haemodilution occurs, which is accompanied by a gain in weight, and conversely with potassium such few observations as we have made suggest slight haemoconcentration with loss of weight. Though, in the normal subject, changes in blood-volume are readily compensated for by corresponding adjustments of the vascular bed, it is possible that these mechanisms are impaired in the hypertensive state, and it has been shown by Miller and Williams (1921) that excessive ingestion of water may produce a very marked rise of blood-pressure in hypertensive subjects.

So far as the second of these factors is concerned, namely the force of the cardiac contraction, there can be no doubt that, in the case of potassium, a rise of this ion in the serum is associated with changes in the electrocardiogram suggestive of alterations in ventricular function. This is well shown in the crises of Addison's disease, in which a change in the electrocardiogram is noted in the shape of an increase in the height of the T-wave, which develops with the accumulation of potassium in the serum. This change has been described by one of us elsewhere (Thomson, 1939 *a, b*), and was very noticeable in our two cases of hypertension which received both potassium citrate and potassium chloride with a concomitant fall in the blood-pressure (Figs. 2 and 3). In Addison's disease this alteration in the electrocardiographic complex is not necessarily associated with a fall in

the serum-sodium, and in our hypertensive patients in whom it was present it developed with a normal serum-sodium content. From a careful study of cases of Addison's disease, we are not inclined to associate this change in the electrocardiogram with any change in the blood-pressure. In the rapid changes in the serum-potassium and sodium which occur in this disease, we have noted a considerable fall in the serum-potassium with corresponding changes in the electrocardiogram, which produced no rise in the blood-pressure; for instance, in one patient a fall in the serum-potassium from 23.6 to 15.7 mg. per 100 c.c. with a definite diminution in the height of the T-wave was accompanied by a fall of blood-pressure from 94/66 to 85/50 mm. of Hg and by a decrease in the voltage of the electrocardiogram. Similarly, the variations in the sodium content of the serum are only roughly parallel to the height of the blood-pressure, though we have never seen the blood-pressure restored to a fully normal level in Addison's disease unless the serum-sodium level was above 320 mg. per 100 c.c. Though potassium in large doses is directly poisonous to the perfused heart, such changes as occurred in the T-wave of the electrocardiogram of these patients with Addison's disease, were not accompanied by a diminution in the voltage of the QRS complex, and do not therefore necessarily indicate any failure of the force of the ventricular contraction.

Should we argue from this analogy, we have no evidence that the slight falls in blood-pressure which occurred in our hypertensive patients on potassium medication are due to a central action on the heart, since in Addison's disease the changes in the electrocardiogram due to accumulation of potassium in the blood are not necessarily associated with a fall in pressure.

If we rule out the possible central action of potassium on the force of the cardiac contraction, such small changes in pressure as we have observed might be due either to changes in the peripheral tonus or to oligæmia. Between these two possibilities we are unable at present to distinguish, though potassium is stated to raise the blood-pressure in animals by increasing the arteriolar tonus (Mathison, 1911; McGuigan and Higgins, 1935). In the case of the sodium salts, no changes in the electrocardiogram were present, and there is therefore no indication that such small changes in the serum-sodium as were produced exercised any effect upon the heart-beat.

Summary

1. The serum of patients suffering from essential and malignant hypertension tends to show a lower level of potassium than that of patients with a normal blood-pressure on the same diet; this is especially marked in malignant hypertension.

2. Low levels of serum-sodium are not infrequent in malignant hypertension.

3. Administration of sodium salts raises the blood-pressure of hypertensive subjects, while potassium salts have the opposite effect. These alterations

are slight, and the amounts of the salts required to produce them are unlikely to be taken in a freely chosen diet.

4. Attempts at depletion of the body sodium were without effect on the blood-pressure.

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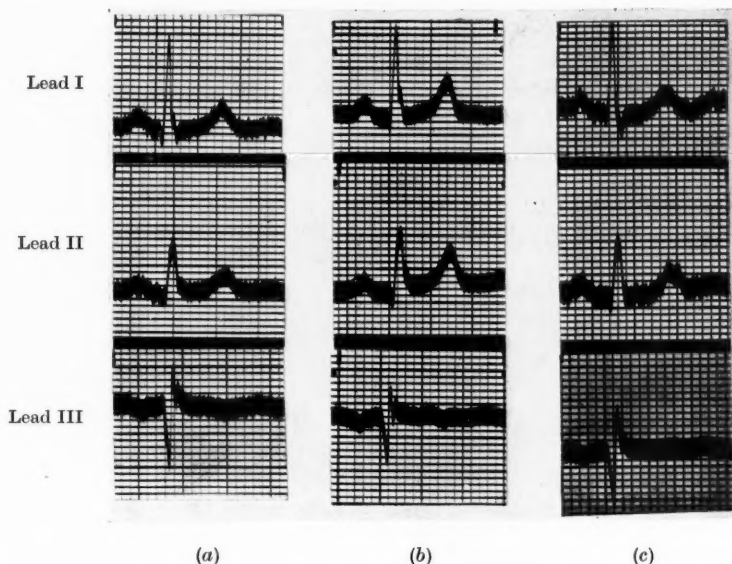


FIG. 2. Electrocardiograms in essential hypertension; (a) March 10, 1939 (serum-potassium 15.5 mg. per 100 c.c.); (b) March 24, 1939, the day on which the administration of potassium was stopped, the patient having received 210 gm. of potassium citrate and 105 gm. of potassium chloride since March 10 (serum-potassium 21.2 mg. per 100 c.c.); (c) March 31, 1939 (serum-potassium 15.3 mg. per 100 c.c.)

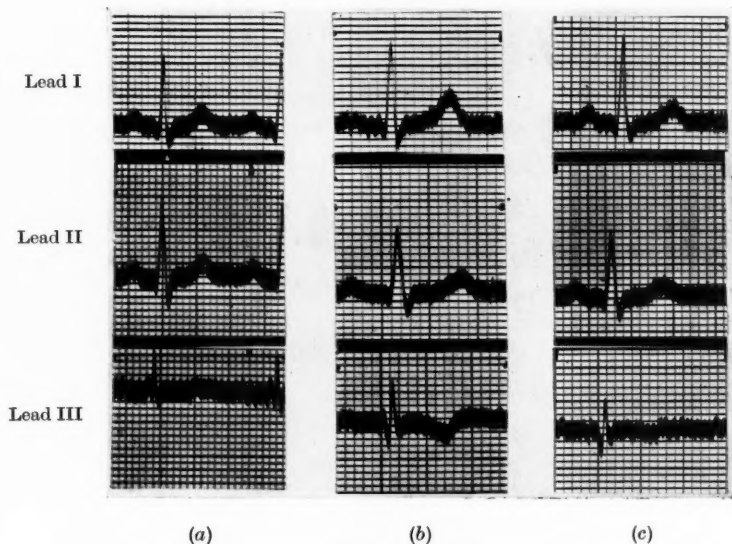


FIG. 3. Electrocardiograms in essential hypertension; (a) January 13, 1939 (serum-potassium 17.2 mg. per 100 c.c.); (b) February 3, 1939, the patient having received 195 gm. of potassium citrate and 100 gm. of potassium chloride between January 13 and 27 (serum-potassium 21.8 mg. per 100 c.c.); (c) February 10, 1939 (serum-potassium 16.5 mg. per 100 c.c.)

PROCEEDINGS OF THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

1939

THIRTY-THIRD ANNUAL GENERAL MEETING

THE THIRTY-THIRD ANNUAL GENERAL MEETING was held in Birmingham on Friday and Saturday, May 26 and 27, in the Chemistry Theatre of the University. The attendance book was signed by 184 members. The proceedings began at 10 a.m.

The President, Professor J. A. Nixon, was in the Chair.

Death of Honorary Member. The death of Sir Robert W. Philip was recorded with regret, the President referring to his eminence in his profession and his presidency of the Association at Edinburgh.

The Minutes of the last Annual General Meeting, having been published in the *Quarterly Journal of Medicine*, were taken as read and confirmed.

The Treasurer presented the Annual Accounts, which showed a balance of £482 6s. 4d. He pointed out that expenditure was likely to increase in the near future, owing to the meeting in London and the need for a new index for the *Quarterly Journal of Medicine*. It was agreed to deposit £300 in the Post Office Savings Bank.

Selection of Place of Meeting for 1940. The London members of the Executive Committee had invited the Association to meet in London in 1940 and an invitation had been received from Dr. George Graham suggesting that this meeting should take place in St. Bartholomew's Hospital and Medical College. These invitations were unanimously accepted.

Quarterly Journal of Medicine. The Secretary reported that Professor T. R. Elliott had resigned from the post of Editor to the *Quarterly Journal of Medicine* and that the Editors recommended the appointment of Dr. J. Crichton Bramwell and Professor A. W. M. Ellis as Editors. These appointments were unanimously approved by the meeting.

Election of Officers

President. Professor J. G. Emanuel was elected President. On his election he took the Chair, and expressed the thanks of the Association to the retiring President, Professor J. A. Nixon.

Election of Officers, Executive Committee, Honorary Members, Extra-Ordinary Members, and Ordinary Members then followed.

Executive Committee

President. Professor J. G. Emanuel.

Treasurer. Dr. H. Letheby Tidy.

Secretary. Professor L. J. Witts.

Members for England:

Dr. J. Murray Bligh.

Dr. George Graham.

Dr. F. G. Hobson.

Dr. C. E. Lakin.

Dr. H. J. Starling.

Professor O. L. V. S. de Wesselow.

Members for Scotland :

Professor L. S. P. Davidson.
Dr. A. Goodall.
Professor A. W. Harrington.

Members for Ireland :

Professor G. Bewley.
Dr. R. H. Micks.
Dr. S. I. Turkington.

Honorary Member :

Professor J. A. Nixon (President 1938-39).

Extra-Ordinary Members :

Professor T. Beattie.
Sir Farquhar Buzzard.
Professor T. R. Elliott.
Dr. G. S. Haynes.
Dr. C. M. Hinds Howell.
Professor W. T. Ritchie.
Dr. Cecil Wall.

Ordinary Members :

William Brockbank, M.D., Assistant Physician, Manchester Royal Infirmary.
Cuthbert Leslie Cope, D.M., Assistant to Nuffield Professor of Clinical Medicine, Oxford.
Harold Percival Himsworth, M.D., Professor of Medicine, University College Hospital.
Claude Blaxland Levick, F.R.C.P., Senior Assistant Physician, St. George's Hospital.
Robert Alexander McCance, M.D., Reader in Medicine, Cambridge.
John McMichael, M.D., Reader in Medicine, British Post-Graduate School of Medicine.
Albert Victor Neale, M.D., Assistant Physician, United Hospital, Birmingham.
Eric Gordon Oastler, F.R.F.P.S., Assistant Physician, Glasgow Royal Infirmary.
Patrick Theodore Joseph O'Farrell, F.R.C.P.I., Physician, St. Vincent's Hospital, Dublin.
Donald Uvedale Owen, M.D., Assistant Physician, Liverpool Royal Infirmary.
Edward Johnson Wayne, M.D., Professor of Pharmacology, University of Sheffield.

SCIENTIFIC BUSINESS

Friday Morning

1. PROFESSOR M. L. OLIPHANT (introduced by PROFESSOR J. G. EMANUEL) discussed *Some Possible Clinical Applications of Modern Physics*. The study of nuclear physics has opened up great possibilities in medicine through the discovery that radioactive substances can be produced artificially. These can replace radium with great advantage in a number of cases, and, as 'indicators', give detailed information of metabolic processes in biological material. Neutron radiation produced by the cyclotron has possibilities as a therapeutic agent in cancer treatment.

DR. S. R. METTIER described three cases of leukaemia under his care in San Francisco which had been treated with radioactive material from the cyclotron; the results had been disappointing. DR. H. L. TIDY referred to earlier experiences with thorium which had not fulfilled its therapeutic promise. DR. F. PARKES WEBER felt that the cure of leukaemia was not to be found in this direction.

2. DR. A. P. THOMSON and DR. H. HUMPHREYS (introduced) described a case of *Spontaneous Hypoparathyroidism with an Account of the Condition of the Teeth*. Low calcium tetany had been present for twelve years and subcapsular opacities that required the extraction of the lens. Parathormone gave relief for four and a half months but the patient then became immune to it. Calciferol, in doses of about a quarter of a million units weekly, had not relieved her. An attempt at grafting a parathyroid adenoma had failed, but a successful result had been obtained in another case which was later shown. DR. H. HUMPHREYS demonstrated that the way in which dentine was laid down was a very sensitive record of parathyroid function.

DR. A. P. THOMSON also referred to the group of three cases with fever, eosinophilia, abdominal symptoms, and histological changes in one case suggestive of tularaemia, which he described to the Association two years ago. He was now satisfied that they were cases of fluke infestation, and he described a dermatological test which he hoped might prove useful in similar syndromes.

3. DR. E. P. SHARPEY-SCHAFER (introduced by PROFESSOR F. R. FRASER) discussed *Pituitary Inhibition by Oestrogens in Castrate and Menopausal Subjects*, and the effect of the oestrogens on the urinary creatinine of castrate and menopausal women was reported. The urinary creatinine was used as an index of pituitary overactivity, since there is excessive excretion in acromegaly, and experimental evidence suggests that such excessive excretion might be associated with the pituitary gonadotrophic hormone. In the menopausal subjects during the control period, the amount of urinary creatinine excreted daily tended to fluctuate, but when oestradiol benzoate was injected in doses of 100,000 i.u. daily, creatinine excretion became constant at the lower level of fluctuation. This result is similar to that obtained on injecting oestradiol benzoate into cases of acromegaly, and demonstrates in an objective manner the depression of the physiologically overactive pituitaries of these menopausal subjects by large doses of the oestrogens. The results in castrates were similar and even more striking. Confirmatory evidence was obtained in collaboration with DR. I. W. ROWLANDS, for it was possible to show that an extract of urine of one of the castrate women normally gave a potent gonadotrophic response when tested on rats, but gave no response when collected during the period of oestrogen injection. Preliminary observations also suggested that the human anterior pituitary obtained *post mortem* might fail to show any gonadotrophic activity when there had been prolonged and heavy oestrogen administration before death.

4. DR. N. HAMILTON FAIRLEY discussed the *Chemical and Clinical Significance of Methaemalbumin (Pseudo-methaemoglobin)*. Methaemalbumin is a brown extracorporeal pigment found in the plasma in haemoglobinurias and certain haemolytic anaemias. When associated with oxyhaemoglobin a composite spectrum results resembling intracorporeal methaemoglobin, with which it has been confused in the past. It is readily differentiated on the Hartridge reversion spectroscope (α band 6230 Å) and by concentrated ammonium sulphide, with which it forms a haemochromogen (Schumm's test). It is synthesized from crystalalbumin and alkaline haematin. Its behaviour in the ultracentrifuge and cataphoresis tube indicates a chemical union. In man it is formed when alkaline haematin is injected intravenously or whenever much blood is destroyed in the circulation.

DR. P. MANSON BARR remarked that this paper was but another example of how the study of tropical diseases led to discoveries of fundamental importance and added that the best place to study tropical diseases was in London. PROFESSOR L. J. WITTS asked whether the presence of methaemalbumin in a reasonably fresh blood sample indicated that haemolysis had occurred in life, and DR. HAMILTON FAIRLEY assured him that this was so, provided the specimen had not been incubated.

5. DR. C. NEWMAN described *The Clinical Use of the Differential Estimation of Bile Pigments*. Whether bilirubin exists in two different chemical forms or not, some sera give a biphasic van den Bergh reaction, and from them one pigment can be extracted with chloroform and one cannot. By taking advantage of this difference in solubility, it is possible, by a simple method, to estimate quantitatively the differently reacting pigments present. In simple obstructive jaundice, it is the prompt-reacting pigment only which is increased; the delayed-reacting pigment remains normal in amount. In toxic-infective jaundice both are increased, and in infective hepatitis ('Catarrhal Jaundice') the delayed-reacting pigment falls to normal long before the jaundice fades. In chronic obstructive jaundice, on the other hand, the delayed-reacting pigment rises *pari passu* with the failure of liver function produced by prolonged back pressure in the ducts. It is therefore possible to differentiate between catarrhal jaundice and other forms at any stage, and to tell accurately how long it is safe to leave a duct obstruction unrelieved by operation. A form of catarrhal jaundice due to simple obstruction can also be identified.

PROFESSOR J. W. MCNEE stressed the value of serial rather than single observations. SIR ARTHUR HURST supported the laevulose test, and said that avertin was a liver poison which should be avoided in jaundice. DR. PARKES WEBER inquired about the

significance of the green colour in the urine which was obtained with the urobilinogen reagent in obstructive jaundice. DR. R. COOPE pointed out that liver damage was often out of proportion to the jaundice, but DR. NEWMAN replied that the test was specially valuable in these cases.

6. DR. T. W. LLOYD (introduced by PROFESSOR L. G. PARSONS) discussed the *Late Prognosis of Icterus Gravis Neonatorum*. Eleven out of 27 children, the survivors of 52 consecutive cases, were found to have developed severe late complications. Prolonged jaundice and/or white stools indicated a bad prognosis. Kernicterus was the most common sequel, while green teeth (2 cases), epilepsy (1 case), and hepatic cirrhosis (2 cases) also occurred. Two cases of osteodystrophia fibrosa with skin pigmentation and precocious puberty in the female were reported. Examination of liver function after apparently complete recovery in seven cases suggested that cirrhosis may develop later in life in some cases.

DR. J. M. H. CAMPBELL congratulated the morning's speakers on having provided better entertainment than the programme had promised. DR. F. J. NATTRASS also spoke.

2 p.m. to 3 p.m.

Clinical cases at the Queen Elizabeth Hospital and demonstrations in the Departments of Pathology and Physiology, Medical School Buildings.

3 p.m. Afternoon Session

1. DR. E. P. POULTON discussed the *Clinical Importance of Local Tissue Anoxia*. It is considered that while the arterial blood is normally saturated with oxygen the tissues are desaturated owing to resistance to diffusion inwards of oxygen. Cases of the condition have already been described mostly as 'anoxaemia', so the significance of the true condition has not been realized. Rheumatic myocarditis is a notable example. In an oxygen tent the patient feels better, the temperature and pulse fall, murmurs become modified, the size of the heart diminishes, and the electrocardiographic signs improve. Twenty-six cases have been studied with a number of rheumatic controls not treated with oxygen.

2. DR. GILBERT HALL (introduced by DR. T. L. HARDY) reported cases of *Tuberose Sclerosis, Rheostosis, and Neurofibromatosis*. The literature concerning the occurrence of bony lesions in association with tuberose sclerosis was reviewed briefly and details of two further instances were given. In the first case, that of a man aged 34 years, the bony lesions were symmetrical and affected the skull and upper extremities; their similarity to lesions described by other authors was mentioned and the suggestion was made that they were due to neurofibromatosis existing in association with tuberose sclerosis. In the second case, that of a boy aged 16 years, the bony lesions were confined to the radial part of the right hand and were characteristic of rheostosis. The association of tuberose sclerosis with rheostosis and neurofibromatosis was explained on the basis that all three disorders were developmental tissue dysplasias.

3. DR. W. RITCHIE RUSSELL and DR. A. C. P. CAMPBELL (introduced) described the clinical features of 18 cases of *Wernicke's Encephalopathy*. The disease occurred usually in association with chronic gastro-intestinal disturbance. Symptoms included mental confusion, disorientation, hallucinations, sleep disturbances, nuclear ocular palsies, loss of vision, and respiratory paralysis. There is reason to suppose that recovery may occur. The disease is probably a deficiency disease.

DR. R. S. ALLISON described a case of Wernicke's encephalopathy from hyperemesis gravidarum. DR. C. P. SYMONDS pointed out that the mental state was highly characteristic, inasmuch as there was no clouding of consciousness and the disorientation was the result of the loss of memory.

DR. A. C. P. CAMPBELL said that recovery might occur, and DR. H. M. SINCLAIR thought that nicotinic acid was more likely to be curative than vitamin B₁.

4. DR. R. G. HENDERSON (introduced by PROFESSOR L. J. WITTS) recorded *Experience with Apparatus for Artificial Respiration*. A number of slides of various types of apparatus used for prolonged artificial respiration was shown. Some of the advantages

and disadvantages of the Drinker type, the Bragg-Paul, and the cuirass respirators were given and the relative merits of positive and negative pressure machines discussed. It was stated that while respirators were of the utmost value in some instances, their scope of application was decidedly limited and their indiscriminate use not devoid of danger. It was stressed that the results of treatment were greatly influenced by careful attention to details of nursing technique and general management, and it was pointed out that this attention could best be secured in specialized centres where experienced medical, nursing, and engineering staffs are concentrated.

DR. A. G. ANDERSON complimented DR. HENDERSON on his work for artificial respiration.

DR. W. EDGECOMBE thought that machines employing partial enclosure were the obvious solution and PROFESSOR R. V. CHRISTIE defended the Bragg-Paul pulsator. DR. W. S. C. COPEMAN inquired about methods of training personnel and PROFESSOR L. J. WITTS said that the number of cases was so small that skill could not be acquired unless treatment was centralized.

5. DR. R. E. SMITH reported two cases of *Paralysis of the Deltoid Muscle after Transfusions or Inoculation*. The first was a man who, from the age of 24 until his death at the age of 36, suffered from severe attacks of haematemesis and melaena. When aged 28 he was given a blood transfusion from a compatible donor and subsequently developed paralysis of the right deltoid. He was given another transfusion when aged 31 and developed paralysis of his left deltoid. There were no other signs of serum sickness. He died from a dissecting aneurysm which ruptured into his pleura. The theory was advanced that the cause of the paralysis was a stretching of the circumflex nerve as it travelled round the shoulder joint. The second case was a boy of 14 who was given 5 c.c. of anti-scarlatinal serum prophylactically in the gluteal muscles. Seven days later he had a severe urticarial rash and pains in the joints. When these subsided it was noticed that the right deltoid was paralysed. Recovery was complete in three months.

DR. C. P. SYMONDS said that the nervous symptoms pointed to a radicular origin and he suggested that a latent virus was stirred to activity by the injection.

6. DR. L. B. COLE discussed the *Prognosis of Tetanus*. This was based on a series of 43 consecutive cases treated on the same general lines. The importance of age, sex, general physical fitness, and the severity and site of the wound were first considered. Of 38 males, 19 recovered, and of five females, all recovered. The length of the incubation period is only a rough guide to prognosis, but when this is less than seven days the prognosis is bad. Severe and fatal cases, however, often occur with an apparently longer incubation period because the actual time of infection or of germination of spores is not known. The 'period of onset' is a better guide and cases do not often recover if this is less than 48 hours, the average duration of life in such being twice the period of onset. If it is over 48 hours the prognosis is good. In all these patients, after the onset of trismus, there was considerable delay before treatment was started and in more than half this exceeded two days. Prophylactic antitoxin must be repeated after severe or very septic wounds to afford protection.

DR. H. L. TIDY stressed the inadvisability of thecal injection of antitoxin and remarked on the occurrence of ketonuria in fatal cases.

Annual Dinner

The annual dinner was held in the Great Hall of the University of Birmingham. The President, PROFESSOR J. G. EMANUEL, was in the Chair. The official guests included the Lord Mayor of Birmingham, the Lord Bishop of Birmingham, the Vice-Chancellor of the University, the Principal of the University, the Dean of the Faculty of Medicine, Alderman W. A. Cadbury, and Sir Harry Vincent. There were present 138 members and guests.

Saturday, 10 a.m., Morning Session

1. PROFESSOR W. N. HAWORTH (introduced by PROFESSOR L. G. PARSONS), discussed *Problems of Synthetic Chemistry in Relation to Therapeutics*. The prerequisite for a successful synthesis of a substance is a knowledge of the molecular architecture gained by the breakdown of the molecule and the structural study of its component

parts. The next stage is that of selecting such building units of appropriate structure and reactivity as will achieve in a final synthesis the same molecular architecture. The problem is not usually so simple as this statement implies. Substances possessing identical structures may have their groups differently distributed in space; a vital factor in relation to physiological activity. Molecules which are mirror images of one another, but are otherwise identical, may have a widely different therapeutic value. Thus the synthetic *d*-form of ascorbic acid was found to be physiologically inactive, whilst the synthetic *l*-form had all the activity of the vitamin. The same comparison can be made between *d*- and *l*-adrenaline. Lacto-flavin (vitamin B₂), when first its synthesis was attempted, was found to differ from the synthetic product merely by a deflexion from right to left of a single hydroxyl group. The synthesis was achieved by adjusting the spatial direction of this hydroxyl group. Among other examples quoted were androsterone and isoandrosterone, which differ enormously in activity for the same reason. Finally, the immunological value of a synthetic pneumococcus antigen was shown to depend on the spatial arrangement of a comparatively small grouping of a biuronic acid residue.

2. DR. K. D. WILKINSON spoke on *Withering and His Original Cases*. Dr. William Withering, a Birmingham physician, discovered the use of digitalis as a diuretic in 1775. He introduced this drug into practice, using first the infusion and later the powdered leaves. His observations were so exact that they taught the dosage, the dangers, and the indications for the use of the drug. He published his book on the foxglove in 1785, enumerating 216 cases, and little has been added to our clinical knowledge of digitalis and its effects since this date. Withering died in 1799 of pulmonary tuberculosis after a prolonged illness.

DR. R. D. GILLESPIE suggested that anthropological studies might give the clue to the choice of digitalis for trial.

3. DR. J. CRIGHTON BRAMWELL and DR. A. MORGAN JONES (introduced) reported a case of *Alcoholic Beri-Beri Heart* in a man of 36 who was suffering from acute heart failure with urgent dyspnoea and extensive oedema. There was a history of chronic alcoholism and gross dietary deficiency. He was successfully treated with parenteral vitamin B₁ and discharged cured seventeen days after admission to hospital. The diagnosis of the condition was discussed.

DR. R. PLATT suggested that the actual volume of fluid consumed was an aetiological factor in the dropsy and DR. K. D. WILKINSON described cases which had been cured merely by stopping alcoholic refreshment. DR. J. SPEARES described the case of a patient who had died despite the reduction of his intake from 35 to 21 bottles of whisky weekly.

DR. H. L. TIDY was surprised that the heart was not more enlarged to the right. DR. PARKES WEBER inquired as to the propriety of salyrgan in these cases. SIR ARTHUR HURST reminded the meeting that Dr. R. T. Williamson of Manchester had described this type of heart failure many years ago and had advised testing the tendon reflexes in obscure cases of heart failure. PROFESSOR L. J. WITTS thought that reduction of the fluid intake to normal was an important element in the patient's cure as the dose of vitamin B₁ had been very small. PROFESSOR R. A. PETERS pointed out that the idea behind high dosage was to promote absorption and phosphorylation; he thought salyrgan would be dangerous as mercury was a cell poison. DRS. C. S. UNGLEY and E. P. POULTON also spoke.

4. DR. W. S. C. COPEMAN discussed *The Arthritic Sequelae of Pneumatic Drilling*. He had found as the result of an investigation of two series of men working with pneumatic tools that arthritic sequelae were rare, although vasomotor phenomena were of common occurrence. This finding was confirmed by a study of the literature of the subject. Joint lesions due to this cause were first described by Holzmann, and as the result of his work were scheduled under the German Workmen's Compensation Act in 1929. Only 833 cases came under this heading, however, in the whole of Germany in the years 1930-34. The changes found appeared mostly to affect the radial side of the wrist, the trapezium and lunate bones. A form of myositis ossificans affected the region of the elbow joint, and the speaker described a case of calcification of the sub-acromial bursa. No X-ray changes affecting joints were found in men who had had less than four years in this occupation.

DR. H. L. TIDY thought that the chief sufferers from pneumatic drills were those who had to listen to them. DR. F. PARKES WEBER inquired about the development of

riziform bodies from the joint dust. Warming to his subject, he said that calcarious bursitis was so infrequent in pneumatic drill operators that their work seemed actually to be a prophylactic against it. He had thought that if the vasomotor sequelae of using pneumatic drills were due to cold, they would be affected by climate, but his letter of inquiry about Italian road-builders in Ethiopia had not been answered. DR. C. P. CLOAKE inquired about the morbid effect of the Raynaud's phenomenon on the hands, but DR. COPEMAN replied that there was no correlation between the vascular and arthritic lesions.

5. DR. NOAH MORRIS and DR. A. S. ROGEN recorded some observations on *The Action of Calcium in Patients with Heart Failure*. Intravenous administration of calcium gluconate to patients with cardiac decompensation led to a slowing of the heart-rate in about 80 per cent. of cases. Patients with regular rhythm were more affected than those with irregular heart action; in the former the percentage slowing was proportional to the original rate. Previous atropinization of the patient prevented the slowing effect of the calcium. When the blood-viscosity was high in these patients it tended to be reduced, at times markedly, after the administration of calcium. Elevation of the serum calcium by parathormone appeared to sustain the diuretic action of mersalyl. Administration of tincture of digitalis led in about 70 per cent. of cases to an increase of serum calcium. The results obtained by calcium therapy were discussed, and it was concluded that in patients with regular rhythm who had not responded well to digitalis the administration of calcium was worthy of trial as a therapeutic measure.

DRS. PARKES WEBER and GEORGE GRAHAM discussed this communication.

6. DR. J. G. SCADDING and DR. PAUL WOOD (introduced by PROFESSOR F. R. FRASER) described *Systolic Clicks due to Left-sided Pneumothorax*. An account was given of a clicking sound during cardiac systole, best heard near the apex-beat, occurring in cases of shallow left-sided pneumothorax, and sometimes audible to the patient or to bystanders. Three cases of this syndrome had been observed by the authors, and several others reported to them. The production of similar sounds by the induction of very shallow artificial pneumothorax was described. These sounds must be distinguished from those due to mediastinal emphysema, and from those described as systolic gallop. The mechanism of production of the sounds was discussed.

DR. K. D. WILKINSON emphasized the importance of crunching sounds in mediastinal emphysema, where they might be mistaken for pneumopericardium.

In the subsequent discussion, in which DRS. R. COOPE, F. H. YOUNG, W. MACADAM, M. DAVIDSON, and SIR WALTER LANGDON BROWN took part, the consensus of opinion was that the clicking sounds in small pneumothoraces were not due to adhesions.

7. DR. H. J. STARLING described a case of *Syphilis of the Lungs* in a patient, Mrs. C., who had been twice married. She had a son and a daughter by her first husband, and a daughter, now 18, by her second husband, a retired sergeant-major, whom she married in 1920. At some period after her second marriage she had sore throats and later, some 'chest trouble' suspected to be tubercular; but at no time did she have any cough or sputum. For the past three years she had been bedridden with arthritis of both knees. About October 1938 her doctor discovered gummatous ulceration of the knee-joints, shins, back, and left shoulder. A blood Wassermann test proved to be strongly positive. Treatment by large doses of potassium iodide nearly cleared up the skin lesion. On admission to hospital the right chest was flattened and dull to percussion, and loud tubular breathing with grossly increased pectoriloquy and vocal resonance was heard over the upper one-third, with multiple fine crepitations over the rest of the lung and at the left base. X-rays showed extensive fibrotic changes of the right lung, the heart was pulled over to the right as well as the trachea, and the right arch of the diaphragm was pulled up to the level of the eighth rib. X-ray films of the right knee-joint showed gummatous infiltration of the lower end of the femur involving the patella.

DR. S. W. PATTERSON showed lantern slides of the pathology of pulmonary syphilis. SIR ADOLPHE ABRAHAMS, and DRS. PARKES WEBER, R. E. SMITH, and W. BOXWELL, gave examples to show that the condition was not excessively rare and that it commonly occurred in patients who were riddled with syphilis. DR. L. G. PARSONS, however, described a case in which it was an isolated manifestation of syphilis acquired by extra-genital infection.

2 p.m. to 3 p.m.

Parties were conducted over the new hospital and medical school, and demonstrations were given in the Departments of Pathology and Physiology.

3 p.m. Afternoon Session

1. DR. S. J. HARTFALL discussed *The Source of Bleeding in a Hundred Fatal Cases of Gastro-duodenal Haemorrhage*, 73 males and 27 females. Peptic ulcer was responsible for the bleeding in 96 (60 gastric, 32 duodenal, and four jejunal) and haemorrhagic gastritis in four. The distribution, size, and shape of the ulcers was discussed. Of the chronic ulcers 40 were gastric, 31 duodenal, and four jejunal. There were 19 acute or subacute gastric ulcers and one acute duodenal ulcer. Complications present, previous and terminal gastric operations, previous gross haemorrhage and healing, and the vessels involved were discussed. In 20 cases there were multiple active ulcers, while scars of old ulcers were present in 57. Gastroscopy in haematemesis in relation to these findings was discussed.

2. SIR ARTHUR HURST and DR. G. A. M. LINTOTT (introduced) described two phenomena. (1) *Haematemesis caused by Aspirin*. A man who had had several attacks of haematemesis without indigestion was in the habit of swallowing unbroken aspirin tablets for migraine. Gastroscopy showed a normal mucosa; swallowed fragments of aspirin were seen to be gripped by the mucous membrane, which was red and haemorrhagic in the neighbourhood of the fragments, two of which were stained bright red by effused blood. (2) *Subacute Gastric Ulcer with Histamine-Refractory Achlorhydria Changing to Hyperchlorhydria after Treatment*. A hitherto unrecognized form of subacute gastric ulcer associated with achlorhydria has recently been described by Rodgers and Avery Jones. The ulcer is often multiple and is too small and superficial to be recognized with certainty with the X-rays, but it presents a characteristic gastroscopic picture. A case was described, in which treatment by diet and lavage resulted in healing of the ulcer and the development of hyperchlorhydria, in spite of the fact that the achlorhydria was previously refractory to histamine.

3. DR. E. BULMER discussed *The Gastroscopic Study of Radiologically Negative Dyspepsia*. He referred to the unsatisfactory state of diagnosis of the dyspepsias, and mentioned that more than one-third of his 'gastro-duodenal' group of 1575 patients were left with most indefinite diagnoses after investigation by radiology and other means. Gastroscopy had been used as a routine method of further investigation in 147 patients of this group, and in more than half of them organic disease of the stomach was found of a type which seemed to account for their symptoms. In most a gastritis was present, but a few unsuspected ulcers and one inoperable cancer were brought to light. The speaker stressed the impossibility of a certain diagnosis of gastritis without gastroscopy, and he was of the opinion that the method, although tedious and uncomfortable for the patient, was of much importance in gastric investigation when radiology was negative or inconclusive.

These three communications were discussed together. PROFESSOR J. W. MCNEE added an analysis of another 62 fatal gastro-duodenal haemorrhages. DR. A. P. THOMSON emphasized the possibility of severe and wellnigh fatal haematemesis after aspirin, and DRs. PARKES WEBER and H. L. TIDY mentioned the likelihood that other drugs had the same effect. SIR EDMUND SPRIGGS also spoke.

4. DR. BRUCE NICOL (introduced by PROFESSOR L. S. P. DAVIDSON) discussed *The Effect of Diet, Alkalies, and Atropine on Gastric Secretion in Peptic Ulcer with Hyperchlorhydria*. The mean 24-hour gastric acidity was compared in 19 ulcer patients on one-hourly milk diets with either two-hourly meals or light diets of four meals a day. The amounts of atropine and alkalies recommended by Hurst were given with each diet. Complete neutralization of the gastric contents was never obtained, but the acidity on two-hourly and light diets was in every case lower than on hourly feeds. Even when atropine was given in toxic doses (1/50 gr. four-hourly) no constant or marked effect on mean gastric acidity was observed. Large doses of aluminium hydroxide gel or magnesium trisilicate (one drachm every hour) did not materially affect the mean acidity. When milk was administered by continuous drip, satisfactory control of the gastric acidity was obtained. Accordingly it is suggested that the failure of hourly feeds or hourly doses of antacid to control acidity is due to rapid emptying of the stomach. Lastly, larger meals containing more protein were of more value in neutralizing gastric acidity than small frequent feeds.

SIR ARTHUR HURST pointed out that exactly opposite results had been obtained by himself and Sippy, and suggested that perhaps Scotch people drank their milk in one gulp. DR. GEORGE GRAHAM also spoke.

5. DR. T. L. HARDY, speaking on *Aerogastrie Bloquée*, defined it as a condition in which large quantities of air were taken into the stomach by aerophagy, but could not be removed by the normal process of eructation. The possible causes were mentioned. Two cases illustrating the typical clinical and radiological features were then described in detail and illustrative radiograms shown. The appearance known as the cascade stomach was well marked in each case and was shown to be due to pressure of a splenic flexure distended with gas. It was suggested that this type of cascade or pressure hour-glass stomach was an important factor in producing the 'aerogastrie bloquée'.

SIR ARTHUR HURST showed radiograms illustrating the same condition.

At the conclusion of the meeting SIR WALTER LANGDON-BROWN proposed a hearty vote of thanks to the Birmingham members for their hospitality, congratulating them on the success of the meeting and mentioning especially the services of the President, PROFESSOR J. G. EMANUEL, the Local Secretary, DR. J. M. SMELLIE, and the Dinner Secretary, DR. T. L. HARDY. This was carried with acclamation.

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